TRANSACTIONS

OF THE

American Clinical and Climatological Association

THE SIXTY EIGHTH ANNUAL MEETING

October 31 November 1 2 1955

The Homestead Hot Springs Virginia

VOLUME LXVII

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Earl A Bruns Edwin A Locke	1926
John A Lichty George M Piersol	1927
George D Porter James S McLester	1928
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Charles D. Parfitt	1934
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James J. Waring	1941
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T. Grier Miller	1947
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Maurice C. Pincoffs	1949
John T. King	1950
John Minor	1951
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Hugh J. Morgan	1953
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J. R. Leaming, E. T. Bruen	1889
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DECEASED MEMBERS

*ORIGINAL MEMBERS

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James E Paullin Thomas C Kelly	1933
Charles H Cocke Roy D Adams	1934
Thomas Klein John F King Jr	1935
Alvah H Gordon Chauncey W Dowden	1936
John B Hawes II Ralph H Major	1937
John H Musser James J Waring	1938
Robert Wilson Russell L Haden	1939
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Maurice C Pincoffs Francis M Rackemann	1942-6
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Julian M Ruffin William B Terhune	1951
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William Duffield Robinson	1918-21
Cleveland Floyd	1921-30
Francis B Trudeau	1930-46
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Date of Elect		Date of Death
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19	R ats Stew rt B Atlanta	1941
19	R r Will m Hr n Boston	1954
1891	R son B m New York	1924
1890	R so Will m D Ph ladelph a	1935
1907	Rochest r Del c B ff lo	1929
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1890	R ers F J A Den er	1922
1921	Ro n Aug st Leys Sw tze la d	1954
1914	P ss J mes Bro M treal	1919
1 91	Ru o C n Switze la d	1901
1920	R rt Steele Wash gton D C	1949
1904	S wich Fi m M Lo do	1918
1919	S w r n John P Cle la d	1943
18 4	Sch ertle n E war R Kansas C ty	1918
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1906	Sc zzen H w C P tt burg	191
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1401	F w He De s	1935
1919	S ell A G Alb q er que	1922
1893	c e Fa ver L Detro t	1913
1919	Sm Burt R Detro t	1950
1919	S w J mes S Boston	1954
1900	Smith A A ex b New York	1915
1885	Smith A n w H C neva N Y	1910
1919	Smith Ch s E St P l	1921
1927	Sm th J m H Richmond	1953
189	So z S E wis Colorado Spri g	1906
192	So W lam B New H ve	1939
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1911	Str z W ea R Hartf d	1942
1919	Stew rt D A M nette M toba	1937
1909	St M rtin L A he lle	1940
1890	Stell Alf Ph l d lph a	1900
1904	St Arth r h Em m m C tre	1952
1915	St W o J Pasadena	1943
1932	St W m C L k woo N J	1951

Date of Elect		Date of Death
1 0	Sto rt A C Salt Lak C ty	1933
1911	Stu rt Pro R rt F T ronto	1940
1893	Sex e ks n Sm m Lo do n	1930
1910	Sw n J hn B Roches N Y	1919
1901	Sw W ll H w C lorad pri gs	1942
1892	T o H Le venw rt St Paul	1932
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1 9	T m J Ca r Balt more	1925
1910	T m J n D Wash ngton	1946
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1883	T r t F w n L Sa so Lak	1915
1 1	T o n J Hi o so L ncol N b	1929
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1894	W n e J mes B Philadelph	1919
191	W F r R D C r C mb dge	1931
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189	Wes n S n H man London	1918
1895	W ee, Leo New York	191
1894	Wes house B F Brooklyn	1891
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1911	W t Wi am C es Wash gto	191
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1904	W n John A Den	1911
189	W lli Ch rl T London	1912
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1939	W m H n r B Philadelphia	1943
1919	W lso C son B lt more	193
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1 91	W lso J mes C Phila l lphia	1934
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1905	W m W n Wash gton	1911

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1935	HA F D M D I m	1946
19	H R OW WI IAS P Bo ld C lo	19 5
1933	HARROP G ORGE A P ceto	1945
1891	H T J H A Colorad Sp ngs	19 5
19	H W M M Ott w	19 3
1914	HAWE Jo N B Boston	1933
1896	HEFFRON Jo N L Sy c	19 4
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191	HEN RSON PR Y N N w H n	1944
1893	HIN AL GUY Charl tt s ll V	1948
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1894	I G LS E F ET HER Ch cago	1918
1889	JACOBI A RAH M New Y k	1919
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19 9	JE O ALPH U F D trot	1945
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1917	M O R Y W P rtland Oreg	1931
188	M THOM J Ph l delphia	1918
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1894	MCGAHA C R E F A k n	1910
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1915	MER R WIL I H P tt b gh	1933
1905	M LL R J t AL X R N w Y k	1948
19 8	M S Y R B lt m re	1949
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190	N CHOLS F P rtl nd M	1944
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1885	P M A B A A bo	1888
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19 1	P J M F Atla t	1951
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1 95	P IPS W M F R Charlesto	1935
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1901	R H M C W Wasl gt	1929

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18 4	R son B r y New York	1924
1890	R son W 1 m D Ph lad lphia	1931
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1895	Rochest n T mas F B ff lo	1897
1899	R Jo O Rochester	1915
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1923	R t A g st Ley witzerland	1954
1934	Ross J es Bre o M t eal	1942
1 91	Pr C Sw t l d	1901
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1911	W tt W ll m Cr es Washi gto	194
1919	W He B De	1949
1904	W l J h A De	1911
1897	W l C es T Lo d n	1912
1898	W m H r Boston	1926
1895	W l m H a r F Brooklyn	1937
1911	W L l R N w Y k	1934
1907	W L L B Lo d n	1939
1938	W m n H a B v Philad lphia	1943
1910	W lso G no Balt more	193
1889	W lson H M J Pu blo Colo	1894
1884	W lso J mes C Philad lphia	1934
191	W lso R Charlest S C	1946
1913	W N a l K C mb dg	195
1946	Wood tt R T Ch cag	1953
1917	W g S Alm t Lond	194
1933	W J r H New York	193
1901	W m W y r Wash gto	1911

Date of Election		Date of Death
190	H ll Jo iah N D se	1939
1912	Ha t ian Loui B lt mo e	1946
1893	H ce Irw n H Lak wood	19 9
1935	H es Fr c M D l m	1946
1922	Harlow Will m P Bo ld C lo	19 5
1933	Harrop Georg A Pr ceton	1945
1891	H rt Jo eph A Colorad S g	1925
19??	H rt William M Ott w	19_3
1914	H we J n B 2nd Bosto	1938
1896	Heffro Jo L Syrac use	19 4
1918	H Fred H T d	1946
1912	Hen r on Prof Ya Ne H	1944
1893	Hin dale Cty Cha l ttes lle V	1949
1902	Ho l nd Henry W P lm Sp gs	191
1889	Hodges W ll D Bost n	1892
1914	H l n G Wa ter De er	1934
1884	Hoop Fr lin H Bosto	1892
1932	Houston Wi i R A st	1953
1905	H l on John H N w Y k	1915
1894	Hud on F D n v N w Yo k	189
189	Hutc i on Willia F P d nce	1893
1884	I gal E Flet n Cl cag	1918
1890	J co A r ham N w Y k	1919
1895	Jarvi W C New York	1895
19 ?	Jen Alp e F D trot	1945
1901	J nning C r e (D t t	1936
1881	Jo o Ho A Cl go	1891
1915	Joh t n Coll H (nd R p d	1936
1884	J h ton W W W t gto	190
191	Jones I do r N h ll	1951
1931	Jon T D c tt N w Y k	1954
1910	K l (o D Wh t S lph Sp ng	1916
1885	Ke ing Jo n M Ph l d lph a	1893
19 6	K l Al B lt	194
1901	Ki o H M o L berty N Y	191
1899	I er Ar old C Sw t la d	1942
191	Klot W ter C N w Y k	1941
1884	K Fre r ck I Boston	1909
19 1	Krau A en K Pro d ce	1941
1884	Kretsc m I el H Brooklyn	1891
1903	K r D Bra Ph lad lph a	1916
188	L w ib S mu W N rth tto	1915
19 9	L w e C Henr Brookl	1945
1884	Le m o J m R N w Y k	1893
1 09	L Fe n Eg rt N w Y k	1914
19??	I m n I c I N w O leans	193
1909	Li to W C e Ed t gh	1953
1919	Litc tt b Majo L w c Ph la l l	1930
1914	L chty J hn A Clift S gs N Y	193
18 0	I ol Rufu P N w York	190?
191	Llo d J J Roches	1944
1 ?0	Low r H C w la t	1894
1916	Lo oc r W L T Lee M ss	1 53
1885	Lo gwell R M ha t F	1894
1884	Loom Al n L N w Y k	1895
1 96	Loomi H r P N w Yo k	190?
1913	Lo Fre T Bost n	1941
1904	Lowm J H Cle l l	1919
193	M cke z C orge M e Coopers t wn	195
1938	Mack Tho a T We tport C nn	1955
1902	Mary l Philip Atl t c City	1939
191	M rvin I o Char e F Wash gt D C	1943
191	M on Ra r C P rtl d Oreg	1945
191	M t R y W I tl d Oreg	1934
189	M ss Tho J Ph l d lphia	1919
190?	McB e J e H Pasad	19?8
1930	McCa P ul Press t Sa t m N C	194?
1894	McCahan Ch e F A ke	1910
1921	M Lest J i S B m gham	1951
1915	M ccr Wil i H P tt b gl	1933
1905	M J me Alexan N w Y k	1948
19 8	Mi er S dn y R B lt more	1949
1934	M ll Ch rles Wilson T cso	1945
1899	Mi o C l L Ash ville	19?8
19 5	M ot Geor e R Brookl Mass	1950
1931	Mono Gr Fr ce	193
1917	Mon go r ry C ia le M Oteen N C	193
1891	Moore H B C l rado Sp g	1900
19 3	M Jo n W lker Lo is ll Ky	195
19 3	Moorman L w J Oklal C ty	1954
189	M o n E h lb rt C Wash gto	1891
1909	Morg n Jam e D Wash gton	1919
1919	Mou t W n B M t l N J	1949
18?0	M h l J C St Lo	1900
1921	Mu Jo n H N w O l La	1947
1885	Muss n J O Ph l l lp l	1912
190	N ho F es P rtl l M	1944
1917	N W lt r I N w Y k	1944
1888	Nunn R n J S l	1911
1884	*O ne H r S Los A g l	1912
1888	Ott E O Bost	1933
1934	P oc B c W I tt f l I Mass	1935
1885	P m r A B A n A bo	188?
1913	P rr tt (l n D T ro to	1951
1 88	P J n B l gt	1890
191	P rson Ro t C Sara c Lak	1921
19?1	P n J m F Atla ta	1951
189	P Al rt (Wash gt	1914
1900	P rc E S I l la l lp l ia	1904
1884	P pp W l m I h lad lph a	1 9
1906	P J Iro I ce R I	1949
1914	I rp S R rt W Scotla l	1939
1 95	P ps W m F R Cha lest	1935
189?	I tt W B B lt more	19?2
191	I J Woo Sara ac Lak	1951
19??	P r B ttle Creek	1940
1904	P W m H A be lle	1905
1905	P J H B ff k	19?3
18 1	Q m (ta I New Yo k	1921
1 91	R m ((New York	1910
1919	R W r L Cana lag N Y	1919
1891	R B m Alhamb ra Cal	1917
1890	R J C lorado Spr ng	189
1885	R C C New Y k	1915
1923	R H M Detro t	19?6
1901	R ow (W Wash gt	19?9

Date of Election		Date of Death
1904	R h a A J Canada	1922
191	R o Paul H New Y k	195
19	Po kern St w rt R Atlant	1941
192	Ro Willi m H r Bost	1954
1884	R son Be y New York	1924
1890	R s Wi li m D Philadelphia	1911
190	Rochester Dr c r B ff l	1979
1885	Rochester Thom F B ff lo	189
189	R J O Rochester	1915
1 90	Ro rs E J A Denver	1972
1923	R lli a, Ar er Leys n Sw zerla l	1954
1934	Pow J mes Bro r Montreal	194
1891	Re C rl Switzerla d	1901
1920	R tten St rli g Wash gt D C	1949
1904	S w ch Fl m M London	1919
1915	S wy r Jo P Cle la l	1945
1881	Sch erele Edwa B, K nsas C ty	1910
1905	Sch tter r W m C Princeto	1933
1928	Schlett H w C P tt b rgh	194
1901	eSchw rt E A Wash gt n	1904
1901	S w ll H ry D nv r	19 4
1919	S ttle A G Alb quer	1972
1894	cr r E ert L Detroit	1913
1910	She y Bert R Detro t	1950
1919	S m J m S Bosto	1951
1890	Smith A A ex p New Y k	1915
1885	Smith And w H (ne N Y	1910
1919	S ith C ler E St P l	1971
19	Smith J mes H Richmo d	1953
188	Snell S F w s C l rado p g	1909
19	Sc r W l oB N w H en	1939
1925	S c T m P B ltimore	1955
1911	S n W a r R H rtf r l	1942
1912	St w rt D p A N tt M t ba	193
1909	St M rtin L A he ll	1940
1890	St r A er Philad lphia	1900
1904	St Arthur K F m m Ce tre	195
1915	St Willa J Pasadena	1911
1892	Sto Willi m C L ewoo N J	1894

Date of Elect		Date of Death
1890	Storn rt A C Salt Lake C ty	1903
1911	Strr rt Pro R rt F T ronto	1940
1878	Sc la D Sept mc Lo d	1950
1910	w r J w W Rochester N Y	1919
1901	Sw Will H w r Colorad Spri gs	1932
1 9	T tl H Lo cert rt St P ul	1932
1896	T lor J M so Philadelphia	1931
189	T m J C r Balt more	1895
1910	T mas John D Wash gt	1946
1931	T as Jam s Dowl g New H	1942
1885	Tur r E w L Sar nac Lak	1915
1881	Tr l J H so Lincol N b	1909
1885	V n B r n W C Balt more	189
1891	W J m s B Philad lphia	1910
1917	W P R D Cotreey C mb idg	1931
191	W rs B rtram H New Y rk	19
191	W e C B Colorad Spr ng	1919
189	W e F r Her ma Lo do	1919
1885	Were L on p N w York	191
1881	West ood B F Brookly	1891
1896	Whitcomb H nry H N towy P	1916
1911	W tt Will m C rl s Washingto	191
1899	W tn y H rt B Den e	1949
1904	Wil x J hn A De er	1911
189	W m C es T Lo do	1912
1929	W l m H to Boston	19
1885	W li m H rt F Brooklyn	193
1911	Will m L r R N w Y rk	1934
190	Will m Leo ar L B Londo	1939
1935	W lm n Har B Philad lphia	1943
1910	W lso C de B lt more	1932
1889	W lso H M J Puebl Colo	1894
1884	Wilson J mes C Philad lphia	1934
191	W lso Ro rt Charlest n S C	1946
1913	Woo N than el K C mb dge	195
1916	Woo rt R T Chicago	1953
191	W rt Alm roth Lo do	194
1913	W croft Joh H New York	193
1901	W m W l Washingto	1911

PRESENT MEMBERS

Honorary Members

Elected

1946 Blalock, Alfred Johns Hopkins Hospital Baltimore 5 Maryland
1949 McNee Sir John Headbourne Worthy House Kings Worthy Winchester Hants England
1926 Rist, Prof Edouard 5 rue Magdebourg Paris France
1910 Rogers Sir Leonard C I E Melville Hotel Falmouth Cornwall England
1902 Weber F Parkes 68 Harley House Regent s Park London N W 1 England

Emeritus Members

1921 Adams Roy D 1150 Connecticut Avenue N W Washington 6 D C
1922 Amberson James Burns Bellevue Hospital New York New York
1932 Amoss Harold L 68 Deerfield Drive Greenwich Connecticut
1930 Austrian Charles R 1417 Eutaw Place Baltimore 17 Maryland
1917 Baetjer Walter A 1115 St Paul Street Baltimore Maryland
1925 Beardsley E J G 1919 Spruce Street Philadelphia Pennsylvania
1931 Bortree Leo Williams 2104 North Cascade Avenue Colorado Springs Colorado
1919 Bray Harry A New York State Hospital Ray Brook New York
1934 Burwell C Sidney Peter Bent Brigham Hospital Boston Massachusetts
1914 Byers John Roddick Gananoque Ontario Canada
1925 Cecil Russell L 33 East 61st Street New York New York
1919 Chadwick Henry D 141 Worcester Lane Waltham Massachusetts
1925 Cooke Robert A 60 East 58th Street New York New York
1917 Craig Frank A 429 Montgomery Avenue Haverford Pennsylvania
1918 Crankshaw Charles W 201 Quaker Lane South West Hartford Connecticut
1925 Dochez Alphonse R 630 West 168th Street New York 32 New York

Elected

1929 Dowden Chauncey W 603 [illegible] Building Louisville 2 Kentucky
1934 Erickson Reuben Johan R F D Slingerlands New York
1927 Evans Frank A Western Pennsylvania Hospital Pittsburgh 24 Pennsylvania
1931 Farley David LaBaume 1429 Larchwood Avenue Philadelphia Pennsylvania
1910 Floyd Cleaveland 246 Marlboro Street Boston Massachusetts
1929 Fremont-Smith Maurice 12 Hereford Street Boston Massachusetts
1911 Fulton Frank Taylor 273 Bowen Street Providence Rhode Island
1927 Gibbes James Heyward 1417 Hampton Avenue Columbia South Carolina
1921 Gorham J Whittington Public Health Research Institute City of New York Inc Foot of East 15th Street New York New York
1909 Griffin Walter Alden Sanatorium Sharon Massachusetts
1932 Hayes John N 19 Academy Street Saranac Lake New York
1927 Herrmann George R John Sealey Hospital Galveston Texas
1923 Kelly Thomas C 105 School Lane Germantown Pennsylvania
1932 Kern Richard A Temple University Hospital 3401 North Broad Street Philadelphia 40 Pennsylvania
1925 King John T 1210 Eutaw Place Baltimore Maryland
1907 Kinghorn Hugh M 14 Church Street Saranac Lake New York
1922 Klein Thomas 250 South 18th Street Philadelphia Pennsylvania
1932 Lathrope George H 2 Elm Street Morristown New Jersey
1914 Lee Roger I 264 Beacon Street Boston Massachusetts
1932 Levy Robert L 730 Park Avenue New York 21 New York
1909 Locke Edwin Allen Wilton New Hampshire
1936 Lunt Lawrence K Double Four Ranch Wheatland Wyoming
1907 Lyman David R Wallingford Connecticut
1925 Major Ralph H University of Kansas School of Medicine Kansas City Kansas
1935 Manier John Owsley 416 Doctors Building Nashville Tennessee
1929 Marcy C Howard 2851 Bedford Ave Pittsburgh 19 Pennsylvania
1928 Mayer Edgar 850 Fifth Avenue New York New York
1929 McCann William Sharp 260 Crittenden Boulevard Rochester New York
1932 McClellan Walter S 406 Whitehead Circle Chapel Hill North Carolina

PRESENT MEMBERS

HONORARY MEMBERS

Elected

1946 BLALOCK, ALFRED, Johns Hopkins Hospital Baltimore 5 Maryland
1949 MCNEE SIR JOHN Headbourne Worthy House Kings Worthy Winchester Hants England
1926 RIST PROF EDOUARD 5 rue Magdebourg Paris France
1910 ROGERS SIR LEONARD C I E Melville Hotel Falmouth Cornwall England
1902 WEBER F PARKES 68 Harley House Regent's Park London N W 1 England

EMERITUS MEMBERS

1921 ADAMS ROY D 1150 Connecticut Avenue N W Washington 6 D C
1922 AMBERSON JAMES BURNS Bellevue Hospital New York New York
1932 AMOSS HAROLD L 68 Deerfield Drive Greenwich Connecticut
1930 AUSTRIAN CHARLES R 1417 Eutaw Place Baltimore 17 Maryland
1917 BAETJER WALTER A 1115 St Paul Street Baltimore Maryland
1925 BEARDSLEY E J G 1919 Spruce Street Philadelphia Pennsylvania
1931 BORTREE LEO WILLIAMS 2104 North Cascade Avenue Colorado Springs Colorado
1919 BRAY HARRY A New York State Hospital Ray Brook New York
1933 BURWELL C SIDNEY Peter Bent Brigham Hospital Boston Massachusetts
1914 BYERS JOHN RODDICK Gananoque Ontario Canada
1925 CECIL RUSSELL L 33 East 61st Street New York New York
1919 CHADWICK HENRY D 141 Worcester Lane Waltham Massachusetts
1925 COOKE ROBERT A 60 East 58th Street New York New York
1917 CRAIG FRANK A 429 Montgomery Avenue Haverford Pennsylvania
1918 CRANKSHAW CHARLES W 201 Quaker Lane South West Hartford Connecticut
1925 DOCHEZ ALPHONSE R 630 West 168th Street New York 32 New York

Elected

1929 DOWDEN CHAUNCEY W 605 Fincastle Building Louisville 2 Kentucky

1934 ERICKSON REUBEN JOHAN R F D Slingerland New York

1927 EVANS FRANK A Western Pennsylvania Hospital Pittsburgh 24 Pennsylvania

1931 FARLEY DAVID LABARVE 4129 Larchwood Avenue Philadelphia Pennsylvania

1910 FLOYD CLEAVELAND 246 Marlboro Street Boston Massachusetts

1929 FREMONT-SMITH MAURICE 12 Hereford Street Boston Massachusetts

1911 FULTON FRANK TAYLOR 27 Bowen Street Providence Rhode Island

1927 GIBBES JAMES HEYWARD 1417 Hampton Avenue Columbia South Carolina

1921 GORHAM I WHITTINGTON Public Health Research Institute City of New York Inc Foot of East 15th Street New York New York

1909 GRIFFIN WALTER ALDEN Sanatorium Sharon Massachusetts

1932 HAYES JOHN N 19 Academy Street Saranac Lake New York

1927 HERRMANN GEORGE R John Sealey Hospital Galveston Texas

1923 KELLY THOMAS C 105 School Lane Germantown Pennsylvania

1932 KERN RICHARD A Temple University Hospital 3401 North Broad Street Philadelphia 40 Pennsylvania

1925 KING JOHN T 1210 Futaw Place Baltimore Maryland

1907 KINGHORN HUGH M 14 Church Street Saranac Lake New York

1922 KLEIN THOMAS 250 South 18th Street Philadelphia Pennsylvania

1932 LATHROPE GEORGE H 2 Elm Street Morristown New Jersey

1914 LEE ROGER I 264 Beacon Street Boston Massachusetts

1932 LEVY ROBERT L 730 Park Avenue New York 21 New York

1909 LOCKE EDWIN ALLEN Wilton New Hampshire

1936 LUNT LAWRENCE K Double Four Ranch Wheatland Wyoming

1907 LYMAN DAVID R Wallingford Connecticut

1925 MAJOR RALPH H University of Kansas School of Medicine Kansas City Kansas

1935 MANIER JOHN OWSLEY 416 Doctors Building Nashville Tennessee

1929 MARCY C HOWARD 2851 Bedford Ave Pittsburgh 19 Pennsylvania

1928 MAYER EDGAR 850 Fifth Avenue New York New York

1929 McCANN WILLIAM SHARP 260 Crittenden Boulevard Rochester New York

1932 McCLELLAN WALTER S 406 Whitehead Circle Chapel Hill North Carolina

Elected

1935 McConkey Mack Pine Street Extension Saranac Lake, New York
1925 McMillan, Thomas M, 1901 Walnut Street Philadelphia 3, Pennsylvania
1929 McPhedran Frederick Maurice Germantown Hospital, Penn and Chew Streets Germantown, Philadelphia, Pennsylvania
1917 Meader Charles N 755 Josephine Street Denver Colorado
1922 Metzger Jeremiah 340 N Main Street, Tucson Arizona
1919 Miller, Arthur R Nova Scotia Sanatorium, Kentville Nova Scotia
1932 Miller T Grier 133 S 36th Street Philadelphia 4 Pennsylvania
1909 Miner Charles H 264 South Franklin Street Wilkes Barre Pennsylvania
1934 Minor John 2030 R Street N W Washington 9 D C
1934 Montgomery Lorne C 1414 Drummond Street Montreal Canada
1930 Morgan Hugh J Vanderbilt University Hospital Nashville Tennessee
1932 Morriss William H Gaylord Farm Sanatorium Wallingford, Connecticut
1933 Mulholland, Henry B University of Virginia Hospital Charlottesville, Virginia
1927 Nicholson Samuel T Jr 642 High Street Pottstown Pennsylvania
1921 Packard Edward N 142 Park Avenue Saranac Lake New York
1930 Pepper O H Perry 551 Maloney Pavilion University Hospital *Philadelphia Pennsylvania*
1917 Piersol George Morris University Hospital Philadelphia Pennsylvania
1926 Pincoffs Maurice Charles University Hospital Baltimore 1 Maryland
1917 Porter George D 75 Crescent Road Toronto Canada
1922 Porter William Branch Medical College Hospital Richmond 19 Virginia
1902 Pottenger F M Pottenger Sanatorium and Clinic Monrovia California
1905 Pratt Joseph H 25 Bennet Street Boston Massachusetts
1928 Rackemann Francis Minot 263 Beacon Street Boston Massachusetts
1932 Root Howard F 44 Dwight Street Brookline Massachusetts
1917 Russell Nelson G 135 Linwood Avenue Buffalo New York

Elected

1931 Sevier John Alston 402 Burns Building Colorado Springs Colorado
1915 Shattuck George C Harvard Medical School Boston Massachusetts
1927 Smith F Janney 269 Wimbleton Drive Birmingham Michigan
1932 Smith William Atmar 151 Wentworth Street Charleston South Carolina
1917 Smith William H 262 Commonwealth Avenue Boston Massachusetts
1925 Snowden Roy R 3509 Fifth Avenue Pittsburgh Pennsylvania
1925 Stroud William D 1011 Clinton Street Philadelphia 7 Pennsylvania
1932 Sturgis Cyrus C Simpson Memorial Institute University of Michigan Ann Arbor Michigan
1907 Taylor J Gurney 324 East Wisconsin Avenue Milwaukee Wisconsin
1931 Thomas Henry M Jr 1201 N Calvert Street Baltimore Maryland
1929 Thorburn Grant 1602 Genesee Street Flint Michigan
1920 Trudeau Francis B 105 Main Street Saranac Lake New York
1929 Waring James J University of Colorado School of Medicine Denver Colorado
1928 Wearn Joseph Treolar Lakeside Hospital Cleveland Ohio
1922 White Paul D 264 Beacon Street Boston Massachusetts
1929 Wolferth Charles C 3400 Spruce Street Philadelphia 4 Pennsylvania
1934 Youmans John Barlow Dean School of Medicine Vanderbilt University Nashville Tennessee

Active Members

1946 Abernethy Theodore J 1834 Eye Street N W Washington 6 D C
1940 Adams F Dennette 226 Marlboro Street Boston Massachusetts
1941 Allan Warde B 6 East Eager Street Baltimore 2 Maryland
1953 Allen Edgar V 102–110 Second Avenue Southwest Rochester Minnesota
1952 Andrus Edwin Cowles Johns Hopkins Hospital Baltimore 5 Maryland
1951 Appel Kenneth E 206 Glenn Road Ardmore Pennsylvania
1950 Armstrong S Howard Cook County Hospital Chicago 12 Illinois
1955 Austrian Robert 451 Clarkson Avenue Brooklyn 3 New York

Elected

1946 BADGER, THEODORE L 264 Beacon Street Boston Massachusetts

1935 BAKER BENJAMIN M 9 East Chase Street Baltimore 2 Maryland

1938 BAKER JAMES P Greenbrier Clinic White Sulphur Springs West Virginia

1946 BAKER MYLES P 262 Beacon Street Boston Massachusetts

1934 BARNWELL JOHN BLAIR Veterans Administration Building Vermont and H Street Washington 25 D C

1951 BEAN WILLIAM B Department of Internal Medicine University Hospitals Iowa City Iowa

1951 BEEBE RICHARD T Albany Medical College Albany New York

1953 BERRYHILL WALTER REECE Dean of the Medical School University of North Carolina Chapel Hill North Carolina

1947 BILLINGS FREDERICK T JR Vanderbilt University Hospital Nashville 4 Tennessee

1948 BLAIN DANIEL Room 102 1785 Massachusetts Avenue N W Washington 6 D C

1938 BLAND EDWARD F Massachusetts General Hospital Boston 14 Massachusetts

1936 BLANTON WYNDHAM B 828 West Franklin Street Richmond 20 Virginia

1939 BORDLEY JAMES III Mary Imogene Bassett Hospital Cooperstown New York

1937 BORTZ EDWARD L 2021 West Girard Avenue Philadelphia 30 Pennsylvania

1948 BOSWORTH HOWARD W 1901 Chavez Ravine Road Los Angeles California

1949 BROWN THOMAS McP The George Washington University Hospital 901 23rd Street N W Washington 7 D C

1947 *BROWN W HURST 280 Bloor Street West Toronto 5 Ontario* Canada

1951 BROWNE JOHN S L Room 106 Medical Building 3640 University Street Montreal P Q Canada

1952 BRUES AUSTIN M 1221 East 57th Street Chicago Illinois

1940 BURKE HUGH E 670 Victoria Avenue Westmount Montreal 6 P Q Canada

1952 BURNETT CHARLES HOYT University of North Carolina Chapel Hill North Carolina

1946 BURRAGE WALTER S 530 Dartmouth Street Boston 16 Massachusetts

1948 CAPPS RICHARD B 122 South Michigan Avenue Chicago 3 Illinois

Elected

1935 COOPER, DAVID ALEXANDER 1520 Spruce Street, Philadelphia, Pennsylvania

1954 COURNAND, ANDRE Cardio-Pulmonary Laboratory, Bellevue Hospital, New York 16, New York

1954 CRAIGE, ERNEST Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

1932 CUSHING, EDWARD HARVEY 017 N Street, N W, Washington, D C

1947 DANIELS, WORTH B 1150 Connecticut Avenue, N W, Washington, D C

1954 DELP, MAHLON University of Kansas Medical Center, Kansas City 3, Kansas

1940 DETWEILER, HERBERT K 1007 Medical Arts Building, Toronto, Canada

1949 DEXTER, LEWIS Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Massachusetts

1947 DURANT, THOMAS M Temple University Hospital, 3401 North Broad Street, Philadelphia 40, Pennsylvania

1954 DYER, W WALLACE Bryn Mawr Medical Building, Bryn Mawr, Pennsylvania

1953 EBERT, ROBERT H 950 East 59th Street, Chicago 37, Illinois

1952 ECKBERG, ROGER O Veterans Administration Center, Los Angeles 25, California

1952 ELLIS, DANIEL S 1101 Beacon Street, Brookline 46, Massachusetts

1946 ELLIS, LAURENCE B 319 Longwood Avenue, Boston 15, Massachusetts

1946 ELSOM, KENDALL A Hospital of the University of Pennsylvania, Philadelphia 4, Pennsylvania

1948 EMERSON, KENDALL, JR Peter Bent Brigham Hospital, Boston 15, Massachusetts

1950 EPPINGER, EUGENE C Peter Bent Brigham Hospital, Boston 15, Massachusetts

1936 ERNSTENE, A CARLTON Cleveland Clinic, Euclid Avenue and 93rd Street, Cleveland, Ohio

1937 FARQUHARSON, RAY FLETCHER Department of Medicine, 100 College Street, Toronto 5, Ontario, Canada

1937 FAULKNER, JAMES M Massachusetts Institute of Technology, Cambridge 39, Massachusetts

1949 FEENEY, NEIL 1414 Drummond Street, Montreal, Canada

1951 FERRIS, EUGENE B, JR Grady Memorial Hospital, Atlanta, Georgia

Elected

1951 Findley, Thomas Medical College of Georgia Augusta Georgia

1946 Fisher, A Murray 18 East Eager Street Baltimore 2 Maryland

1941 Fitz Hugh Thomas Jr 2016 Delancey Place Philadelphia Pennsylvania

1950 Flinn, Lewis B 503 Delaware Avenue, Wilmington Delaware

1948 Flippin, Harrison F, Lankenau Hosp Med Bldg City Line and Lancaster Ave Philadelphia 31 Pennsylvania

1954 Forkner Claude E, 107 Chestnut Street Boston 8 Massachusetts

1949 France Richard Thayer V A Hospital Nashville 5 Tennessee

1954 Fullerton Charles W 1414 Drummond Street Montreal 25 P Q Canada

1936 Fulton, Marshall N 124 Waterman Street Providence Rhode Island

1948 Gammon George D University Hospital 36th & Spruce Streets Philadelphia 4 Pennsylvania

1937 Giddings Glenville Doctors Building 478 Peachtree Street N E Atlanta Georgia

1955 Gordon Harry H Sinai Hospital Baltimore 5 Maryland

1949 Graham John R The Faulkner Hospital 1153 Centre Street Jamaica Plain Boston 30 Massachusetts

1951 Greene James Alexander Baylor University College of Medicine Houston Texas

1950 Halsted James A Veterans Administration Hospital Irving Avenue University Place Syracuse 10 New York

1951 Ham Thomas Hale Western Reserve School of Medicine Cleveland Ohio

1946 Harvey A McGehee Johns Hopkins Hospital Baltimore 5 Maryland

1941 Hetherington Hubert W Henry Phipps Institute University of Pennsylvania Philadelphia Pennsylvania

1940 Higgins William H 710–712 Medical Arts Building Second and Franklin Streets Richmond Virginia

1955 Hilleboe Herman E State Office Building Albany New York

1948 Hinshaw H Corwin 490 Post Street San Francisco 2 California

1950 Holmes Joseph H Department of Medicine University of Colorado 4200 East Ninth Avenue Denver 7 Colorado

1946 Howard John Eager Johns Hopkins Hospital Baltimore 5 Maryland

1949 Howlett Kirby S Jr Laurel Heights State Tuberculosis Sanatorium Shelton Connecticut

Elected

1910 Hunt Henry Dunham 590 North Broadway Saratoga Springs New York

1938 Jones Chester M Massachusetts General Hospital Boston Massachusetts

1910 Jones Oswald R 71 East 71st Street New York 21 New York

1937 Kampmeier Rudolph H Vanderbilt University Hospital Nashville Tennessee

1954 Kay Calvin F University of Pennsylvania Hospital Philadelphia Pennsylvania

1933 Keefer Chester S Evans Memorial 65 East Newton Street Boston 18 Massachusetts

1935 King Donald S Hitchcock Clinic Hanover New Hampshire

1949 Kneeland Yale Jr 1010 Fifth Avenue New York 28 New York

1935 Lawrence John Seward U C L A Medical School 405 Hilgard Avenue Los Angeles California

1949 Leavell Byrd S University of Virginia Department of Medicine Charlottesville Virginia

1955 Leonard John C Hartford Hospital Hartford Connecticut

1952 Lewis Howard P University of Oregon Medical School 3181 S W Sam Jackson Park Road Portland Oregon

1953 Logan Victor W Strong Memorial Hospital Rochester 20 New York

1954 Logue R Bruce Emory University Clinic P O Box 459 Emory University Georgia

1955 Loosli Clayton G Department of Medicine University of Chicago School of Medicine Chicago 37 Illinois

1949 Lukens Francis D W The George S Cox Medical Research Institute University of Pennsylvania Philadelphia 4 Pennsylvania

1952 Lyons Richard H State University of New York College of Medicine Syracuse 10 New York

1947 Machella Thomas E University of Pennsylvania Hospital 3600 Spruce Street Philadelphia Pennsylvania

1934 Martin Lay 1201 North Calvert Street Baltimore Maryland

1946 Martin Walter B 521 Wainwright Building Norfolk 10 Virginia

1955 Mason Robert E 9 East Chase Street Baltimore Maryland

1946 Mateer John G Henry Ford Hospital Detroit 2 Michigan

1946 McDermott Walsh New York Hospital 525 East 68th Street New York New York

Elected

1955 McGee, Lemuel C 900 Market Street Wilmington Delaware
1947 McGuire Johnson, Cincinnati General Hospital Cincinnati Ohio
1952 Meade Gordon M Med Center Williamson W Va
1955 Merrill Arthur J 35 Fourth Street N E Atlanta Georgia
1953 Merrill John P 564 Quinobequin Road, Waban Massachusetts
1953 Michael, Max Jr, Lawson V A Hospital Chamblee, Georgia
1947 Middleton William S Apt 912 A 4200 Cathedral Ave N W Washington 16, D C
1946 Miller C Phillip Department of Medicine University of Chicago Chicago 37, Illinois
1953 Mirick George S Baltimore City Hospital Baltimore Maryland
1952 Mitchell Roger S, 4200 East Ninth Avenue Denver Colorado
1947 Mohr Charles F 1540 Sixth Avenue San Diego California
1952 Montgomery Hugh Hospital of the University of Pennsylvania Philadelphia Pennsylvania
1937 Moore Joseph Earle 804 Medical Arts Building Baltimore Maryland
1949 Muschenheim Carl 133 East 64th Street New York 21 New York
1953 Newman Elliot V Vanderbilt University Hospital Nashville Tennessee
1951 Nichols Edward 85 Jefferson Street Hartford Connecticut
1941 Nicholson William McNeal Duke Hospital Durham North Carolina
1950 Orgain Edward S Department of Medicine Duke University Durham North Carolina
1952 Paddock Franklin K 28 North Street Pittsfield Massachusetts
1953 Palmer Walter L 950 East 59th Street Chicago Illinois
1938 Paul John R Yale University School of Medicine 333 Cedar Street New Haven 11 Connecticut
1947 Peck William M McCain North Carolina
1947 Pillsbury Donald M Department of Dermatology and Syphilology University of Pennsylvania Medical School Philadelphia 4 Pennsylvania
1946 Porter Reno R Medical College Hospital Richmond 19 Virginia
1941 Pratt Henry N New York Hospital 525 East 68th Street New York 21 New York
1954 Ragan Charles 620 W 168th Street New York 32 New York

Elected

1946 RICHARDS DICKINSON W Jr Bellevue Hospital New York 16 New York

1946 RIGGINS H McLEOD 140 East 54th Street New York New York

1936 ROSE EDWARD 426 Owen Road Wynnewood Pennsylvania

1950 RUCKS WILLIAM W Jr Oklahoma City Clinic 01 Northwest 12th Street Oklahoma City Oklahoma

1940 RUFFIN JULIAN MEADE Duke University Hospital Durham North Carolina

1949 RUSK HOWARD A NYU Bellevue Institute of Rehabilitation & Physical Medicine 325 East 38th Street New York 16 New York

1951 RUSSELL NELSON G Jr 135 Linwood Avenue Buffalo New York

1947 SCHAFFER ALEXANDER J 1109 St Paul Street Baltimore 2 Maryland

1935 SCHNABEL TRUMAN G 1704 Pine Street Philadelphia Pennsylvania

1952 SCOTT THORNTON 200 West Second Street Lexington Kentucky

1947 SHERMAN WILLIAM B 60 East 58th Street New York 22 New York

1951 SHULL HARRISON JOHNSTON 8307 Vanderbilt University Hospital Nashville Tennessee

1953 SKAVLEM JOHN H 2700 Union Central Building Cincinnati 2 Ohio

1952 SMITH CARTER 1210 Medical Arts Building Atlanta 3 Georgia

1952 SMITH DAVID T Duke Hospital Durham North Carolina

1946 SPINK W W University of Minnesota Medical School Minneapolis 14 Minnesota

1932 SPRAGUE HOWARD BURNHAM 1180 Beacon Street Brookline 46 Massachusetts

1937 STETSON RICHARD P 203 Commonwealth Avenue Boston 16 Massachusetts

1949 STRANG JAMES M Highland Building 121 South Highland Avenue Pittsburgh 6 Pennsylvania

1940 STRAYHORN DAVID 2122 West End Avenue Nashville Tennessee

1946 TERHUNE WILLIAM B Silver Hill Foundation New Canaan Connecticut

1941 THORN GEORGE W Peter Bent Brigham Hospital Boston 15 Massachusetts

1946 TOONE ELAM C Jr 1200 East Broad Street Richmond Virginia

Elected

1949 Tucker, Henry St George, Jr Medical College Hospital Richmond Virginia
1951 Tumulty, Philip A Johns Hopkins Hospital Baltimore, Maryland
1950 Valentine William N, Department of Medicine University of California, Los Angeles 24 California
1955 Vander Veer, Joseph, B, 320 South 9th Street Philadelphia 7, Pennsylvania
1934 Wainwright Charles W, 9 East Chase Street Baltimore Maryland
1941 Walker, Harry, Medical College of Virginia Hospital Richmond Virginia
1936 Warner Wilfred P 230 Rideau Terrace Ottawa Ontario Canada
1951 Warthin, Thomas Angell 810 Neponset Street Norwood Massachusetts
1947 Watson Cecil J, University of Minnesota Hospital, Minneapolis Minnesota
1951 Weinstein Albert 1211 Twenty First Ave South Nashville 12, Tennessee
1947 White Benjamin V 85 Jefferson Street Hartford 8 Connecticut
1940 White T Preston 211 Hawthorne Lane Charlotte North Carolina
1953 Wilkins Robert W Evans Memorial Hospital 65 East Newton Street Boston 18, Massachusetts
1940 Willis Henry Stuart McCain North Carolina
1934 Wilson Julius Lane Henry Phipps Institute 7th and Lombard Streets Philadelphia 47 Pennsylvania
1940 Winkenwerder Walter LaFollette 1014 St Paul Street, Baltimore Maryland
1953 Wolf Stewart University Hospitals 800 N E 13th Street Oklahoma City Oklahoma
1948 Woodward Theodore E 1 Merrymount Road Baltimore Maryland
1938 Wood Francis C University of Pennsylvania Hospital Philadelphia Pennsylvania
1932 Wood J Edwin Jr Box 1668 University Station Charlottesville Virginia
1948 Wright George W St Luke's Hospital 11311 Shaker Boulevard Cleveland 4 Ohio
1954 Wright Irving S 400 Madison Avenue New York 17 New York

Elected

1934 ZINSSER, HARRY F., JR., University of Pennsylvania Hospital, Philadelphia, Pennsylvania.

Number of Members Living

Honorary	5
Emeritus	87
Active	172
Total	264

Elected

1949 Tucker, Henry St George, Jr, Medical College Hospital, Richmond Virginia
1951 Tumulty, Philip A, Johns Hopkins Hospital, Baltimore Maryland
1950 Valentine, William N, Department of Medicine University of California Los Angeles 24, California
1955 Vander Veer, Joseph, B, 330 South 9th Street Philadelphia 7 Pennsylvania
1934 Wainwright Charles W 9 East Chase Street, Baltimore Maryland
1941 Walker Harry Medical College of Virginia Hospital Richmond Virginia
1936 Warner Wilfred P, 230 Rideau Terrace Ottawa Ontario Canada
1951 Warthin, Thomas Angell 810 Neponset Street Norwood Massachusetts
1947 Watson Cecil J University of Minnesota Hospital Minneapolis Minnesota
1951 Weinstein Albert, 1211 Twenty First Ave South Nashville 12 Tennessee
1917 White Benjamin V 85 Jefferson Street Hartford 8 Connecticut
1940 White T Preston 211 Hawthorne Lane Charlotte, North Carolina
1953 Wilkins Robert W Evans Memorial Hospital 65 East Newton Street Boston 18 Massachusetts
1940 Willis Henry Stuart McCain North Carolina
1934 Wilson Julius Lane Henry Phipps Institute 7th and Lombard Streets Philadelphia 47 Pennsylvania
1940 Winkenwerder Walter LaFollette 1014 St Paul Street Baltimore Maryland
1953 Wolf Stewart University Hospitals 800 N E 13th Street Oklahoma City Oklahoma
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Number of Members Living

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Emeritus	87
Active	172
Total	264

MEMBERS PRESENT AT HOT SPRINGS MEETING

1935

Emeritus Members

Austrian Charles R
Burwell C Sidney
Crankshaw Charles W
Fremont Smith, Maurice
Gibbes James Heyward
Gorham L Whittington
Kern Richard A
King John T
Klein Thomas
Levy Robert L
Miller T Grier
Minor John
Morgan Hugh J
Mulholland Henry B
Pincoffs, Maurice Charles
Porter William Branch
Pratt Joseph H
Rackemann Francis M
Root Howard F
Russell Nelson G
Smith F Janney
Stroud William D
Sturgis Cyrus C
Thomas Henry M Jr
Thorburn Grant
Trudeau Francis B
Waring James J
Wolferth Charles C

Active Members

Abernethy Theodore J
Appel Kenneth E
Armstrong S Howard
Badger Theodore L
Baker James P
Bean William B
Berryhill Walter Reece
Billings F Tremaine Jr
Blain Daniel
Bordley James III
Brown Thomas McP
Burke Hugh F
Burrage Walter S
Capps Richard B
Cooper David Alexander
Craige Ernest
Cushing Edward Harvey
Daniel Worth B
Delp Mahlon
Dexter Lewis
Dyer W Wallace
Ebert Robert H
Egeberg Roger O
Ellis Daniel S
Elsom Kendall A
Emerson Kendall Jr
Ernstene A Carlton
Faulkner James M
Findley Thomas
Fisher A Murray
Fitz Hugh Thomas Jr
Flinn Lewis B
Flippin Harrison F
Forkner Claude E
Fullerton Charles W
Fulton Marshall N

Giddings Glenville
Graham John R
Hunt Henry Dunham
Jones Oswald R
Kampmeier Rudolph H
Kay Calvin F
Keefer Chester S
King Donald S
Kneeland Yale Jr
Lawrence John Seward
Leavell Byrd S
Lewis Howard P
Lilienthal Joseph L Jr
Logan Victor W
Logue P Bruce
Lukens Francis D W
Martin Lay
Martin Walter B
Mateer John G
McClellan Walter S
McGuire Johnson
Meade Gordon M
Merrill John P
Middleton William S
Mirick George S
Moore Joseph Earle
Nichols Edward
Nicholson William McNeal
Orgain Edward S
Paddock Franklin K
Palmer Walter L
Rose Edward
Ruffin Julian Meade
Russell Nelson G Jr
Scott Thornton
Skavlem John H
Smith Carter
Smith David T
Strayhorn David
Terhune William B
Toone Elam C Jr
Tucker Henry St George Jr
Tumulty Philip A
Wainwright Charles W
Walker Harry
Warthin Thomas Angell
Weinstein Albert
White Benjamin V
White T Preston
Wilkins Robert W
Willis Henry Stuart
Winkenwerder Walter LaFollette
Wolf Stewart
Wood Francis C
Wood J Edwin Jr
Woodward Theodore E
Wright George W
Wright Irving S
Zinsser Harry F Jr

Emeritus	28
Active	95
Total	123

CONSTITUTION AND BY-LAWS*

CONSTITUTION

Article I.—Name

This Society shall be known as the American Clinical and Climatological Association.

Article II.—Object

The object of this Association shall be the Clinical Study of Disease.

Article III.—Membership

Section 1.—This Association shall consist of *honorary*, *emeritus* and *active* members. The number of active members shall not exceed 175.

Section 2.—The names of new candidates for active membership, each endorsed by three active or emeritus members of the Association, shall be sent to the Secretary within six months after the Annual Meeting. The Secretary shall list these names, make a summary of the candidates' qualifications and mail the list to each active member with the request that comments concerning the candidates be returned to the Secretary for presentation to the Council. The Council will then act upon these at its meeting to be held the evening before the first scientific session. Such as are approved by the Council shall be considered elected.

Candidates for membership shall at the discretion of the Council present a paper to the Association showing clinical study of merit.

Section 3.—Anyone who has been a member in good standing in this Association for twenty-five years is automatically transferred to emeritus membership, and anyone who has been an active member for twenty years in good standing and has attained the age of sixty years shall become an emeritus member by expressing his desire to do so in writing to the Council. Under special circumstances, such as prolonged illness, removal to a far country, retirement from professional activities, or financial distress, the Council may transfer any active member to emeritus membership at any time. An emeritus member shall have all the rights and privileges of an active member including eligibility to hold office, but shall not be subject to the penalties noted in Article III, Section 4.

Section 4.—Any member of the Association absent from the meetings in person or by contributed paper for three consecutive years, without sufficient cause, shall be dropped from the list of members by vote of the Council.

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* *As amended in* 1925, 1929, 1932, 1933, 1934, 1935, 194[illegible] and 1951.

ARTICLE IV —OFFICERS

Section 1.—The officers of this Association shall consist of a *President* two *Vice Presidents* a *Secretary Treasurer* and a *Recorder* who with eight other members shall constitute the *Council* of the Association

Section 2.—*Nominations* The officers including the Council shall be nominated by a committee of five members which committee shall be appointed by the President at the first session of each annual meeting and shall report at the business meeting

Section 3.—*Elections* The election of officers shall take place at the business meeting A majority of votes cast shall constitute an election

Section 4.—The President Vice Presidents Secretary Treasurer and Recorder shall enter upon their duties at the close of the annual meeting at which they are elected and shall hold office until the close of the next annual meeting or until their successors are elected

Section 5.—Members of the Council other than the officers shall hold office for four years two members being elected at each annual meeting

Section 6.—*Vacancies* Any vacancy occurring among the officers of the Association during the year may be filled by the Council

ARTICLE V —DUTIES OF OFFICERS

President and Vice Presidents

Section 1.—The President shall be ex officio Chairman of the Council The President shall be responsible for the program for the number the selection and the arrangement of formal papers and for any informal meetings or round table discussions He shall invite the speakers for the Annual Dinner He may invite guests to any and all parts of the meeting In his absence the senior or the junior Vice President in order shall act for him

Secretary Treasurer

Section 2.—As Secretary he shall attend and keep a record of all the meetings of the Association and of the Council of which he shall be ex officio Clerk At each annual meeting he shall announce the names of all who have ceased to be members since the last report He shall notify candidates of their election to membership He shall send a preliminary notification of the annual meeting two months prior thereto and the program for the annual meeting at least two weeks prior to its assembly to all the members of the Association He shall also send notification of the meetings of the Council to the members thereof At each annual meeting of the Association he shall read the Minutes of the previous meeting and of all the meetings of the Council that have been held during the current year Furthermore he shall read the names of those active and also

ciate members who had failed to attend three consecutive meetings without sufficient cause

Section 3.—As Treasurer, he shall receive all money due and pay all debts therewith He shall render an account thereof at the annual meeting at which time an auditing committee shall be appointed to report

Recorder

Section 4.—The Recorder shall secure the papers read and also proper notes of the discussions thereon and shall superintend under the direction of the Council the publication and distribution of the TRANSACTIONS He shall arrange for a Recorder Stenographer if any

ARTICLE VI.—COUNCIL

The Council shall meet as often as the interests of the Association may require

Four members shall constitute a quorum

It shall have the management of the affairs of the Association subject to the action of the Association at its annual meetings

It shall consider the claims of candidates recommended to it for admission to membership

It shall not have the power to make the Association liable for any debts exceeding in total one hundred dollars ($100) in the course of any one year unless specially authorized by a vote of the Association

It shall have the entire control of the publications of the Association with the power to reject such papers or discussions as it may deem best

It shall have power to nominate active members at the annual meeting

The Council shall have power to invite any gentleman not a member to read a paper at the annual meeting on any subject within the scope of the objects of this Association

The Council shall determine questions by vote or—if demanded—by ballot the President having a casting vote

The Council shall constitute a Board of Trial for all offenses against the Constitution and By Laws or for unbecoming conduct and shall have the sole power of moving the expulsion of any member

The President or any two members may call a meeting notice of which will be transmitted to every member two weeks prior to the meeting

ARTICLE VII.—PAPERS

Section 1.—The titles of all papers to be read at any annual meeting shall be forwarded to the President not later than two months before the annual meeting

Section 2.—No paper shall be read before the Association which has already been printed or been read before another body.

Article VIII.—Quorum

A quorum for business shall be ten (10) members.

Article IX.—Amendment

Section 1.—This Constitution may be amended by four fifths ($^4/_5$) vote of all the members present at an annual meeting provided that notice of the proposed amendment has been printed in the notification of the meeting at which the vote is to be taken.

Section 2.—By Laws may be amended at any business meeting of the Association by a three fourths ($^3/_4$) vote of all members present and voting.

BY LAWS

(*1*) Meetings of the Association shall be held annually.

(*2*) The time and place of the meeting shall be determined by the Council.

(*3*) A Committee of Arrangements shall be appointed by the newly elected President at the end of the Annual Meeting. This committee shall select the hotel, confer with the management about rooms and prices, arrange for the meetingroom, for special luncheons, for special entertainment as necessary, and arrange for the Annual Dinner. The Secretary shall have custody of the lantern.

(*4*) The dues of active members shall consist of an annual assessment not to exceed twenty ($20) dollars. Members in arrears shall not be entitled to vote. Those in arrears for two years may be dropped from membership by recommendation of the Council. Honorary members and emeritus members shall pay no dues.

(*5*) Candidates for membership that have not been favorably considered by the Council within three years shall be dropped from nomination but may be renominated.

(*6*) Vacancies created by increasing the limit of membership (to 175) shall not be filled in excess of five a year.

(*7*) As voted by the Council in 19 6 and practiced since that time, the fund of money known as the Gordon Wilson Fund shall be maintained by the Treasurer. He shall receive subscriptions to this fund and invest them with the approval of the Council. The income from the Fund shall be used for the expenses of the Gordon Wilson Lectureship. The Lecturer shall receive a bronze medal suitably engraved as well as an honorarium

His travel and hotel expenses shall be paid from the income from the Gordon Wilson Fund supplemented if necessary by money from the general funds of the association

(8) Order of business meeting

First day

Minutes of previous meeting
Secretary Treasurer s reports
Recorder s report
Report of Committee of arrangements
Appointment of Auditing Committee
Appointment of Nominating Committee

Second day morning session

Report of Auditing Committee
Election of new members
Report of Nominating Committee
Election of Officers
Other business
Adjournment of business meeting

THE SECRETARY'S REPORT

THE SIXTY-EIGHTH ANNUAL MEETING HELD AT THE HOMESTEAD, HOT SPRINGS, VIRGINIA, MONDAY, TUESDAY AND WEDNESDAY, OCTOBER 31, NOVEMBER 1, 2, 1955

After a lapse of only two years the Association returned to The Homestead, Hot Springs, Virginia, for its sixty-eighth annual meeting on Monday, Tuesday and Wednesday, October 31, November 1 and 2, 1955. No happier time could have been chosen for Hot Springs weather, and though luncheon out of doors at the Casino was not always comfortable, there was sunshine a plenty. A total registration of 123 members was recorded —28 emeritus and 95 active. When to this is added the attendance of 107 wives, the total equals or perhaps exceeds the largest gathering the Association has had in recent years. Letters or telegrams of regret were received from 31 members.

At the scientific meetings held in the Homestead Theater on each of the three mornings, eighteen papers were read and in traditional fashion freely discussed by the members. The Gordon Wilson Lecture was delivered at noon on the second day by Dr. John F. Enders of Boston on the subject "Observations on Certain Viruses Causing Exanthematous Diseases in Man with Particular Reference to the Agent in Measles."

In keeping with the high level of quality always notable in the Climatological scientific program, social activities began on a comparable scale the night before the meeting, when the Nashville members were hosts at a cocktail party in the Virginia Room. Again in traditional fashion on Monday evening the members and wives dined together in the Empire Room and later danced in the Ball Room. On Tuesday evening after cocktails the members and wives dined separately, thereafter to be united for an hour of entertainment which even these minutes in careful detail could not record adequately. The pleasure of hearing Hugh and Bobby Morgan is not easy to come by outside of Nashville, but their hour had come at Hot Springs and with guitar and their happily blended voices they sang the best of their wonderful repertoire of Southern songs and spirituals. This marked a new high in revelation of membership talent. There followed an unusual demonstration of how much can be said by how many in how short a time when President Thomas, without even military discipline, kept each of five members to a delightful five-minute discourse—each with an individual and different style: Dr. Joseph H. Pratt, Dr. Chester S. Keefer, Dr. Walter B. Martin, Dr. William B. Porter and Dr. Yale Kneeland. Following this Dr. Thomas Klein presented to Dr. Pratt in honor of his many years as a member of the Clima

tological a silver bowl, a gift from some of his devoted friends in the Association. Not many evenings have been better spent.

No account of this meeting would be complete without mention of the happy atmosphere created throughout the session by the president, Henry M. Thomas, Jr., master of the light touch and the friendly word. Thanks also should be recorded for the very helpful work of Dr. James P. Baker of neighborly White Sulphur Springs, who served as a local committee on arrangements. No meeting of the Climatological has been more fun, and very few have equaled it.

MINUTES OF THE COUNCIL MEETING

The Council met at 3:10 p.m. on Sunday, October 30, 1955, at The Homestead, Hot Springs, Virginia. Those present were: Henry M. Thomas, Jr., President; James M. Faulkner and Johnson McGuire, Vice Presidents; Marshall N. Fulton, Secretary-Treasurer; David Strayhorn, Recorder; John Minor, J. Edwin Wood, Jr., Cyrus C. Sturgis, Hugh J. Morgan, Francis C. Wood, Robert L. Levy and Howard F. Lewis. Absent: Chester M. Jones.

It was moved by Dr. Faulkner, seconded by Dr. J. E. Wood, that the minutes of the Council meeting held on October 14, 1954, as recorded in the Transactions, Volume 66, be accepted. Motion carried.

The Treasurer's report, as published herewith, was presented. It was pointed out that the increase in cash balance from $64 to $1,069 was due in part to the increase in membership dues from $15 to $20 and to the decreased total cost of the Transactions. It was agreed without vote that the dues should be kept at the present level for at least one more year.

Following a report by the Treasurer of both the Principal and Income Account of the Gordon Wilson Fund, it was moved by Dr. Minor, seconded by Dr. Wood, that the President appoint a Financial Committee to review the portfolio of the Gordon Wilson Fund each year and to report recommendations to the Council. Motion carried.

The Recorder's report was submitted by Dr. Strayhorn. It was pointed out that the cost of the Transactions was considerably less than the year before due to the difference in size of the volume. There was considerable discussion concerning the offer of other printing companies to print the Transactions, and it was agreed without vote to leave the selection of the printer to the Recorder. It was moved by Dr. Lewis, seconded by Dr. Minor, that the Recorder's report be accepted. Motion carried.

Dr. J. E. Wood, Jr. raised the question of publishing in the Transactions each year a brief statement concerning the history of the American Clinical and Climatological Association. It was moved by Dr. Morgan, seconded by Dr. Levy, that Dr. Wood be authorized to prepare such a statement for publication in the Transactions. Dr. Morgan then raised the question of having the Transactions sent to more medical libraries than those who now subscribe to it annually. No action taken.

Under the heading of communications, letters were read by the Secretary from various organizations concerning the Association. No action taken.

In consideration of *the membership of the Association*, the Secretary *reported* that there were at present 262 members in the following categories:

Honorary	5
Emeritus	86
Active	171

The following members had died during the year
Honorary August Rollier Leysin Switzerland
Emeritus William P Finney Jr Lake Geneva Wisconsin
Thomas I Sprunt Baltimore Maryland
Active T Duckett Jones New York New York
Thomas T Mackie Westport Connecticut

The Council voted to approve the request for transfer to emeritus status in keeping with provisions of the Constitution of Dr Walter S McClellan Chapel Hill North Carolina

Letters of resignation were then read by the Secretary from the following active members

Paul B Beeson Ward Darley Charles S Davidson Charley J Smyth Eugene A Stead Lewis Thomas

It was voted to accept with regret these resignations

The Secretary then read a letter from Sir John McNee concerning the honorary members of the Association and their present activities It was recommended by the Council that this letter be read at the first business meeting of the Association

Explanations submitted by members for their absence from annual meetings for three consecutive years were then read by the Secretary and it was voted by the Council to accept the explanations for absence as submitted

There followed discussion concerning the place of the annual meeting for 1956 and 1957 The Council confirmed the vote made a year previously to hold the annual meeting in 1956 at Skytop Lodge Skytop Pennsylvania on November 1 and 3 There followed discussion for the place of meeting for 1957 those locations considered including Hot Springs Virginia Old Point Comfort Virginia Sun Valley Idaho Charlottesville Virginia Ponte Vedra Club Florida Biloxi Mississippi and Point Clear Alabama After due consideration it was voted that the meeting in 195 should be held at The Homestead Hot Springs Virginia on the earliest dates in November or October that would be available to the Association

Following adjournment for dinner the Council reconvened at 8 p m and considered the candidates proposed for active membership The following were unanimously elected as active members

Robert Austrian Brooklyn New York Harry H Gordon Baltimore Maryland Herman L Hilleboe Albany New York John C Leonard Hartford Connecticut Clayton G Loosli Chicago Illinois Robert L Mason Baltimore Maryland Lemuel C McGee Wilmington Delaware Arthur J Merrill Atlanta Georgia Joseph B Vander Veer Philadelphia Pennsylvania

Following the election of members it was moved by Dr Minor seconded by Dr Morgan as follows

A candidate for active membership shall not be nominated or seconded by an officer or councillor of the Association Motion carried

The meeting adjourned at 11 p m

Respectfully submitted
Marshall N Fulton Secretary

First Business Meeting

The first business meeting was called to order at 12 30 p m Monday October 31 by the President Dr Thomas It was voted that the minutes of the previous meeting as reported in the Transactions Volume 66 be approved The Treasurer s report was submitted by Dr Fulton

TREASURER'S REPORT

(as of Sept 30 1955)

Credit	
Balance on hand (Sept 30 1954)	$ 64 23
Dues	3065 00
Sales of Transactions	
To Emeritus Members	280 00
To Libraries	[illegible] 00
Refund from Lake Placid Club (Registration Fees)	373 05
Payment for extra cuts in Transactions	185 00
Canadian check exchange credit	20
Total	4419 48
Debit	
Honoraria (Recorder and Secretary)	400 00
Master Reporting Co	338 55
Stationery Printing Postage and Telephone	38 95
Transactions Vol 66 1954	2607 34
Presidential Paper Cutter	23 00
Banking Service Charges	2 10
Total	3409 94
Balance on Hand (Sept 30 1955)	1009 54
	4419 48

GORDON WILSON FUND

PRINCIPAL ACCOUNT

		Value Sept 30 1955
3000 U S Savings Bonds		
Value Sept 30 1954	$2886 00	
Increased Value 8th year	15 00	$2901 00
20 Shares Standard Oil Co of New Jersey (Cost 5/3/51 1165 28)		2660 00
50 Shares Cleveland Electric Illuminating C (Cost 5/3/51 1090 62)		1825 00
12 Shares Continental Can Co (Cost 11/26/51 519 53)		8[illegible] 00
Balance in Savings Account		87 [illegible]1
Interest on Savings Account		1 31
Total		836[illegible] [illegible]

INCOME ACCOUNT

Credit	
Balance on hand (Sept 30 1954)	301 61
U S Savings Bond Interest	[illegible] 00
Cleveland Electric Illuminating C	68 75
Standard Oil Co of New Jersey	100 35
Continental Can Co	30 00
Interest on Savings Account	4 12
Total	645 83

Debit		
Lecturer (1954)		
Honorarium	$100 00	
Expenses	72 44	172 44
Medal (1955) Engraving (1954)		39 93
Extra cuts in Transactions (1953)		70 00
TOTAL		282 37
Balance on hand Sept 30 1955		363 46

It was moved and seconded that the report of the Treasurer be accepted subject to the report of the Auditing Committee Motion carried Dr Thomas then appointed Dr Richard B Capps and Dr Robert W Wilkins to serve as an Auditing Committee with instructions to report at the next business meeting

The minutes of the Council meeting were then presented by the Secretary Dr Fulton

The Recorder's report was submitted by Dr Strayhorn

RECORDER'S REPORT

Three hundred copies of Volume 66 of the Transactions of the American Clinical and Climatological Association for 1954 were printed by the Ambrose Printing Company and distributed as follows

To Honorary members	5
To Emeritus members	60
To Active members	17
To Libraries	45

The cost of publishing this volume was as follows

DEBIT		
To the Ambrose Printing Company for printing binding and mailing 300 copies of 309 pages	$2 607 34	
To the Master Reporting Company	338 55	
		$2 945 89
CREDIT		
Income from the sale of Transactions		
To Emeritus members	280 00	
To Libraries	72 00	
Payment for extra cuts	185 00	537 00
Net cost of Volume 66 (1954) 309 pp		2 408 89
Net cost of Volume 65 (1953) 383 pp		2 993 7

Respectfully submitted
David Strayhorn Recorder

It was moved and seconded that the report of the Recorder be accepted Motion carried

The President then announced the appointment of a Nominating Committee as follows

Dr C Sidney Burwell Chairman Dr James Bordley III Dr Rudolph H Kampmeier Dr Carter Smith Dr F Janney Smith

The Committee was instructed to report at the second business meeting

Meeting adjourned at 1 15 p m

Second Business Meeting

The second business meeting was called to order at 9 10 a m on Wednesday November 2 by Dr Thomas

Dr Capps reported for the Auditing Committee that the financial statements of the Treasurer had been found to be in order and it was voted to accept the Treasurer s report as submitted

Dr Burwell then reported the following nominations as presented by the Nominating Committee

President Dr Francis C Wood Vice Presidents Dr Francis D W Lukens and Dr J Earle Moore Secretary Treasurer Dr Marshall N Fulton Recorder Dr David Strayhorn Councillors Dr Henry M Thomas Jr Dr William B Bean and to fill out the unexpired term of Dr Francis C Wood to 1957 Dr Johnson McGuire

It was moved and seconded that the nominations be closed and the slate be elected as announced by the Nominating Committee Motion carried

Dr T Grier Miller suggested that a telegram be sent to Dr J Owsley Manier Nashville Tennessee one of the hosts of our Sunday evening gathering expressing the good wishes of the Association and regrets at his inability to attend the annual meeting as planned

It was suggested by Dr John Minor that the membership consider the nomination of candidates for honorary membership in the Association

Note was made by the President of the galley proofs of Rhymes Verses and Epigrams by our honorary member Dr F Parkes Weber which had been received at the time of the meeting

Dr Thomas announced the appointment of Dr Robert I Levy to serve in advisory capacity concerning the portfolio of the Gordon Wilson Fund in accordance with the recommendations of the Council

The meeting adjourned at 9 30 o clock

Respectfully submitted

Marshall N Fulton Secretary

MEMORIAM

WILLIAM PARKER FINNEY JR

By HENRY M THOMAS JR MD

William P Finney Jr died on March 29 1955 at his home in Lake Geneva Wisconsin following years of invalidism from Parkinson's disease To his many friends Bill's death at the age of 66 years seemed a long awaited release from physical and mental suffering and a release to the friends as well whose hearts ached miserably whenever some bright memory brought Bill to their mind

The only son of a Presbyterian minister who in his later years was Professor of English at Lincoln University Bill showed his brilliance early in life and had passed the entrance requirements for Princeton University at the age of 12 He delayed entering until 14 and after graduating with honors spent three years at Beirut Syria where he taught in the Syria Protestant College

Feeling the need to enlarge his sphere of contribution by studying medicine he returned to the United States and after completing a year of premedical work he entered The Johns Hopkins Medical School From the start he excelled and led his class at graduation in 1916 That summer he married his classmate Dr Theodora Wheeler of Bridgeport Connecticut Of their three daughters and two sons one daughter has studied medicine and one nursing After two years in the Department of Pathology with Doctors Welsh Whipple and Winternitz he served in the Medical Corps of the Army during World War I He then became a Fellow at the Mayo Clinic in 1919 where his natural interests led him into the Department of Medicine

Dr Finney's talents lay along clinical lines and he was an expert diagnostician keenly alert to unusual disease entities He was greatly respected by his colleagues An interesting feature of his medical history is his bibliography I should say of course his lack of bibliography for as far as I know he published but two papers one of which reported two years work in an Army research laboratory Because his brilliance did not explore new or original paths he refused to write routine medical articles or talk at County Medical meetings In his spare time he delighted to challenge his friends on the golf links or play chess with cronies with some of whom it was necessary to record the moves by mail to distant parts

He advanced on the staff of The Clinic enjoyed his duties and acquired a large clinical experience At the age of 43 years he moved to Winnetka to enter the practice of internal medicine in Chicago and on

the North Shore This successful and pleasant venture was cut short after a few years by the premature development of Parkinson's Disease His efforts to practice in the face of increasing tremor and dreadful stiffness were heroic and tragic

Bill Finney was beloved by his classmates and associates His intellectual qualities were partially hidden by a charming patina of warm friendship and a lively happy sense of humor He had no faults unless it be a fault to have little worldly ambition or a fault to have no false pride He was a member of the Society of Cincinnati but rarely attended meeting He was a fine simple man

My medical associates have provided many objects of personal admiration and a number of dear friends Bill Finney was one of the earliest admirations and one of the dearest friends

MEMORIAL

THOMAS DUCKETT JONES

By EDWARD F BLAND MD

T Duckett Jones died November 22 1954 at the Johns Hopkins Hospital at the age of fifty five of diffuse vasculitis and malignant hypertension He was born in Petersburg Va descendant of a colonial family long distinguished in medicine His father was a physician his brother is a surgeon a sister is a physician and two other sisters are married to physicians He graduated from the Virginia Military Institute in 1919 and received his medical degree from the University of Virginia in 1923 where he served as an interne and resident In 1925 he was a Dalton Fellow and cardiac resident at the Massachusetts General Hospital and thereafter spent a year as a National Research Council Fellow with Sir Thomas Lewis at University College Hospital in London In 1928 he returned to the House of the Good Samaritan in Boston where he organized the clinics and the research department which he directed for the next twenty years During this period he was also an active member of the Harvard Medical School faculty and of the staff at the Massachusetts General Hospital where under Dr Paul D White's supervision he inaugurated and developed the rheumatic fever clinic As a result of his many and important contributions he became recognized internationally as an authority on this disease In 1947 because of his eminence in the field he was asked to become the medical director of the newly established Helen Hay Whitney Foundation in New York City It was with great reluctance that he gave up his active research career in Boston but the realization of the opportunity offered by his new duties to further the control and prevention of the disease to which he had devoted his life left him no alternative In addition to his many responsibilities in this connection he was president of the American Rheumatism Association a vice president of the American Heart Association and chairman of the association's Council on Rheumatic Fever president-elect of the National Health Council president of the Protein Foundation and chairman of the Committee on Plasma Fractionation and Related Processes at the Laboratory of Physical Chemistry at Harvard University and a member of the Advisory Council of the National Heart Institute

Duckett Jones was in many ways an unusual person His deep loyalty to his friends to his associates and to his profession was his religion His life was devoted to the conquest of rheumatic fever and through his own efforts and those of countless others whom he inspired he well knew that victory was near at hand His last important public appearance was as

the North Shore This successful and pleasant venture was cut short after a few years by the premature development of Parkinson's Disease *His efforts to practice in the face of increasing tremor and dreadful stiffness were heroic and tragic*

Bill Finney was beloved by his classmates and associates His intellectual qualities were partially hidden by a charming patina of warm friendship and a lively, happy sense of humor He had no faults unless it be a fault to have little worldly ambition or a fault to have no false pride He was a member of the Society of Cincinnati but rarely attended meetings He was a fine simple man

My medical associates have provided many objects of personal admiration and a number of dear friends Bill Finney was one of the earliest admirations and one of the dearest friends

PRESIDENT'S ADDRESS

Problems of Post Graduate Medical Education

By HENRY M THOMAS JR MD

BALTIMORE

When last year I was recalled from the supposed security of my Emeritus retreat to serve as the President of our Association I must confess to extreme pleasure and gratification No one who appreciates the cordial friendliness of this organization could miss the glow of satisfaction at being honoured in this way Worthy or not and very humbly it is a proud moment to stand in line with the distinguished list of internists who have presided over the Climatological

When in this very hall twenty four years ago I was elected a member of this society the name was The American Climatological and Clinical Association However at the next meeting Dr Gordon Wilson proposed to amend the name so as to emphasize the clinical aspect of the scientific meetings This change was voted although a great deal of sentiment was expressed in favor of retaining the name Climatological To many of us this name has come to signify a society whose meetings are conducted in an atmosphere of friendship strengthened by common aims and interests an atmosphere free from harsh professional ambition and comfortable in the avoidance of ultra scientific precision and measurement This is not to say that we disapprove of clear scientific thinking or of accurate measurement It is to say I think that we hope to emphasize the additional and not to be lost sight of factors in the practice of medicine encompassed by the term clinical The patient is never very far from our meetings Chemists and physicists respond to the challenge of clinical application

Lest the subject of my remarks this morning had been treated by some former President I read those addresses which I had not actually heard delivered It may interest you to know that from their writing the personality pattern of these Climatological clinicians becomes quite clear Actually this pattern is practically identical with the one ascribed to patients with migraine headaches peptic ulcer hyperthyroidism hypertension coronary artery disease and obesity These men are excessively modest or so they would have one believe They have diplopia in that simultaneously they look far into the past and equally far into the future Occasionally they preach a bit and are a bit pompous There is constant evidence of insecurity leading these Presidents to identify themselves with great clinicians of earlier days whom they describe with apparent intimacy and affection in their address Whether garrulousness is part of

chairman of an international panel on rheumatic fever at the Second World Congress of Cardiology in Washington in September It was shockingly evident to his friends at this time that he was seriously ill but only upon their insistence did he finally seek medical aid He lived only two months longer but to the end it must have been a source of deep satisfaction to know that the studies he started a quarter of a century ago and the interest he inspired in others elsewhere had played such a significant role in the progress of the intervening years In Boston alone there remain 3 000 patients who recall with gratitude and affection his careful and kindly guidance through childhood rheumatism at the House of the Good Samaritan and at the Massachusetts General Hospital

His was truly a dedicated life

Biological Course) and approved in principle by the Medical Faculty[1] They seemed too exacting to be practical and even President Gilman fore saw difficulties in filling the classes Dr Welch is said to have surmised that the first class would consist of a few women only Actually these requirements may have contributed largely to the remarkable immediate success of this new unfettered experiment in medical education Without adequate control it can at least be said that these admission requirements did not cast the prophesied blight on the new institution

The new type medical school aroused criticism from near and far Its graduates were good only for teaching or research but learned nothing practical You could always tell these graduates if they didn t tell you first Before many years elapsed however other medical schools followed suit The contrast between the graduates of this new type medical school and the small proprietory old type schools then existent all over the country was so great that by 1910 as one of our former Climatological presidents has called it the great medical school purge began

The heads of the clinical departments who were dedicated to an enor mous amount of teaching found that they could not give the necessary time to careful supervision of the operation of the university hospital wards to the teaching and to the administration of the department to say nothing of the medical school itself To provide assistants brilliant young men were kept on in what was called the residency for five or six years until they became superior clinicians and teachers This chef de clinique type of thing may have been the beginning of the long residency training program that is now in vogue throughout the country

Heartened by the sudden upswing in the standards of medical educa tion one or two great foundations accepted more armchair theory which in this instance emanated from the preclinical chairs and provided funds to endow a few full time clinical professorships As one medical educator states these po itions had been previously obtainable on the basis of professional pre tige but now were open to young men interested more exclusively in teaching and research One such foundation contributed over the years about one hundred million dollars total in relatively small parcels to a good many different chools to initiate this academic move ment and give it impetus The success of this catalytic contribution is readily apparent when one realizes that now after some forty years of growth the combined medical school budgets of this country for one year alone approaches one hundred million dollars Much of this expense is incurred by the extensive research laboratories which are of course an essential feature of this system The lure of these laboratories and the exciting stimulation of association with a group of scientific explorers are more persuasive to many young physicians than the mundane but never theless gratifying practice of medicine The stimulation filters down to

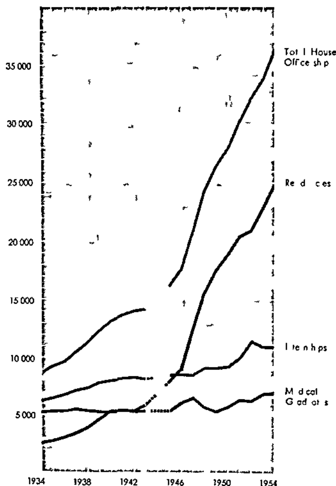
the pattern or of anno domini is a nice question Their repressed resentment subconsciously contributes to the length of their orations Gratefully their little jokes relieve the sombre hue of the mantle of dignity they assume for the occasion An accidental moment of thought reminded me that practically every one of these characteristics had been mentioned to me at one time or another by my own closest personal observer I realized why I had been chosen

This CPP (Climatological Presidential Personality) is to make a pun of a pugilistic phrase 'saved by the bell La belle To the ladies this Association owes its reputation for having the most charmingly gay meetings Through their presence we achieve a very high membership attendance Under their smiles our pleasure is heightened We are grateful and glad that they come to the meetings and we only hope this feeling is reciprocated

Far from the Association of American Medical Colleges and the Council on Medical Education and Hospitals of the American Medical Association I am emboldened to express a few thoughts about medical education Much that I am about to say is known to you, but I hope to point up certain problems which are current and important

Recently pre medical education at the college level and post graduate in the residency training and practice level has been discussed and is being studied It is difficult to find established facts on which to base accurate conclusions as to the value of this or that pedagogical principle or practice but there is no lack of literary effort emerging philosophically from the armchair Even President Pussey when he says that we shall not know fully until 1980 whether our contemporary educational effort has been good implies that it will be a simple matter to evaluate the college product vintage 1955 twenty five years hence I know of no yardstick for such a comparison One should however hesitate to criticize empirical pedagogy since it seems to have led to effective methods In fact to some extent our present large and expensive medical faculties depend on high academic standards forced on the founders of an embryonic institution The board of trustees while hoping to open the Johns Hopkins medical school was confronted by a shrunken financial capital due to unforeseen economic reverses around 1880 When a small group of high minded and clear thinking women came forward with the money necessary to allow the medical school to open they used their influence to establish certain dangerously high requirements To enter this medical school one must have a Bachelor s degree must have had certain college courses in science and two foreign language Women must be admitted on the same footing as men The course was four years study before the M D degree was obtained These requirements were based on courses given at the Johns Hopkins undergraduate department in Group Three (Chemical

training to each individual's own unassisted devices as it was in my father's time? The effect of their remarks has not been apparent. Until about 1946 residency training was limited mostly to the University connected hospitals. While in training these residents accomplished a useful clinical duty for the hospital and school and at the same time had access to their choice of laboratories. Since 1945 the number of approved residencies has increased 224% and roughly 415 of this increase has been in the approved hospitals many of which are University Hospitals.



Borrowed from Dr. James E. McCormack, Associate Dean, Graduate Studies, Columbia University College of Physicians

the student body and imaginative minds are stirred From these laboratories come professors and also trained investigators for the commerce of medicine And from this great new research development has come rapid progress

With the accelerated advance in medical knowledge in all of the preclinical and clinical subdivisions specialization became inevitable That no one specialist could handle what we now call a diagnostic survey entirely by himself became quite evident and in 1918 Dr Lewellys F Barker started a series of talks and papers on the subject of group diagnosis and group therapy The principles which he enumerated nearly forty years ago although vigorously opposed at the time are widely accepted now

In the special field of internal medicine post graduate training has varied throughout the world and various parts of this country Formerly young doctors were given the opportunity to perform clinical duties on the House Staff while maintaining contact with the undergraduate teaching They developed skill by repetitive performance in an environment of large clinical material If they had a gift for research they found time to add this The trend lately is in the direction of relieving the resident or fellow from much of his clinical duties and emphasizing study conferences and research or as Dr McCormack puts it treating (it) as an educational experience

The American Board of Internal Medicine was formed rather late in the general movement of Specialty Boards designed to determine individual competence in any given specialty These Boards are blamed for many present day difficulties encountered by medical schools and hospitals they are scolded for sins they could hardly have committed and influence they do not wield One of the early and vocal critics of the whole Board system and in particular the Board of Internal Medicine was my former friend the late Dr Thomas R Boggs In his Presidential Address[3] before the Association of American Physicians in 1937 he said

We the oldest National society of internists have been and are moving toward a goal of high quality in the field of internal medicine Shall we continue our work as in the past fifty years which has accomplished so much or shall we join in a movement to bring about a millennium by force with the new evils which ever accompany such efforts?

Dr Boggs worried lest residency training be either limited to those few provided with sources of income apart from their personal earning or the school and the hospital be requested to supply this training He abominated standardization Dr Alan Woods in his 1947 Presidential Address to the American Academy of Ophthalmology and Otolaryngology directed his criticisms at the American Board of Ophthalmology There have been several others Did they really hope to leave post graduate

Founded 1886 the Climatological was founded 1884

does the Board find out whether or not he really is this specialist? By examinations since the criteria suggested by Dr Boggs of having the professional qualifications of an individual judged by his associates and teachers cannot be put to practical use

I have heard a great many well informed recent residents state that taking the written examination was one of their most interesting experiences. This examination represents the combined effort of the members of the examination committee aided by other Board members and even occasionally by a dose of rejuvenation from youthful sources As far as written examinations go and surprisingly enough the Board does not think written examinations go very far this is a good and rather forward looking examination An effort is made to equate the relative difficulty of this test from year to year and thus leads to a slight variation in the passing grade The Board is constantly advised by an expert on academic examinations The Librarian of the Board in conjunction with a number of very hard working committee members has performed an excellent not to say monumental service About 1600 candidates annually take the written examination The failure rate is between 45% and 55% including repeaters

On an average 800 candidates qualify annually for the practical examination In the early years this test was confined to two long cases very much as given by the Royal College of Physicians in Great Britain but subsequent modifications have added time for exploring the candidate's own specialty his habits of reading what medical periodicals he prefers what articles he remembers reading recently and similar details that make up an internist Many of these discussions are of great interest and reveal a brilliant mental capacity fully capable of being turned toward clinical medicine but in some cases ones which have diverted too much of the clinical time into research These individuals could if they chose become outstanding internists but will they choose and should they be certified on pure potentialities? In an effort to avoid the prejudices which operate for or against candidates in the hands of any examiner an additional part of the practical examination has been set up in which various clinical and laboratory exhibits are to be marked according to a multiple choice technique The candidates enjoy this they have a sense of security and freedom from stage fright they believe this examination actually is fairer From analysis by experts in the field of academic examination this particular section of the practical examination is found to test some faculty other than bedside clinical ability

From memory I should say very roughly that each year 35% do not pass these practical tests Ultimately however about two-thirds of all

There has been a simultaneous but smaller relative increase in internships and it is fair to say that the reduction in routine work thus afforded to each house officer was for the purpose of allowing him more time for *instruction study* and beginning research as well as a little time to sleep Thus the University hospitals controlled by the professors of clinical subjects have been a major factor in building up this large system of post graduate education Meanwhile the non University hospitals which had or instituted their own residency program are finding it difficult and often impossible to obtain house staffs Even with the service of 6000 foreign trained physicians there are still 8000 vacant house officerships A tremendous effort is being made to improve the educational quality of residencies in so *called* non teaching (i e non university) hospitals and with some success Full time directors of medical education are being employed Interesting experiments are already afoot such as the one in which residents are 'farmed out to non teaching hospitals where they obtain wide responsibility and concentrated clinical experience to the benefit of both resident and hospital The post war increase in residencies and fellowships has produced an unexpected imbalance the correction of which requires wise planning

Why *should not* the Specialty Boards do something about this? Even the critics of the Board of Internal Medicine say that some of the members are nice people Nice but deluded not quite bright and a little blind Actually and quite seriously the Board is concerned over this problem While *I was on the Board its functions were sharply delineated* These were to examine candidates and to certify those who passed the tests Certain broad screening requirements are enforced to eliminate individuals who obviously are not and most probably never will be internists Careful *consideration was given to the possibility of allowing any reputable grad* uate in medicine to present himself for the examinations without fulfilling further requirements This seemed somewhat undignified for an important specialty and totally impractical from the weight of members Although *physicians who have confined their practice* to internal medicine for a number of years may take the examination a shorter and more uniformly successful form of training is through an approved residency followed by two years of practice Whether or not a residency is approved is not the business of the Board This is determined by a council formed from members of the American College of Physicians Association of American Medical Colleges and the American Medical Association The Board is not interested in whether an intern rotates or vibrates or just hibernates He must have had time and opportunity to obtain knowledge and judgement sufficient to become a specialist in internal medicine How

toward the solution of this problem the Specialty Boards can contribute important information

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candidates pass both examinations and are certified It has seemed to us that the very high percentage of failure in the practical examination must indicate a serious fault in the concept of post graduate training How some candidates who pass the rather difficult and very inclusive written examinations can perform so badly at the bedside never ceases to cause amazement to the examiners Our Board hopes to bring to light some helpful information on this subject A study of the correlation of his pre medical, medical and post medical experiences with his behavior on the written examination and the two phases of the practical and bedside examination may at least indicate areas of strength and areas of weakness in the system The foundation has been laid for a statistical study facilitated by the use of IBM punch cards We realize that in terms of modern medical education which process of course is unending the young doctor seven to ten years out of medical school has not reached clinical maturity

Meanwhile to add a simple and hopeful note may I record my belief that those candidates who are thoroughly conversant and practiced in obtaining a good clinical history and can follow it up by a complete routine brisk physical examination which recognizes deviations from normal and explores their ramifications and their meaning such a man I say will have no trouble in passing the present day practical examination

The substance of my remarks leads to certain conclusions in a growing area of medical education In retrospect it seems likely that the modern renaissance in medical education was triggered by a somewhat fortuitous setting of very high academic standards A direct result of the new type University hospital medical school was the development of laboratories for clinical research in most subdivisions of all the clinical departments The upsurge of medical information led automatically to the highly developed system of specialization The residency system begun as an integral part of the clinical management of the wards and supervision of the teaching of the clinical clerks has developed into an important new portion of medical education My experience of six years of examining young internists leads me to believe that many of these residents have missed the basic grounding gained only from wide clinical experience Since the war the amazingly rapid increase in residencies and fellowships in University hospitals and approved non teaching hospitals has led to a temporary imbalance with various harmful effects Since the pattern of residency training is molded in the university hospitals it seems to me essential that the medical school clinical faculties whose members control these residencies become thoroughly aware of the wide implications of post graduate education There is great and immediate need for integration of all post graduate education in teaching and non teaching hospitals and

THE RELATION BETWEEN APPEARANCE AND BEHAVIOR OF THE ISLANDS OF LANGERHANS IN MAN

By F. D. W. Lukens, M.D. and W. Wallace Dyer, M.D.

PHILADELPHIA

Is there any relation between the structure of the islands and their functional capacity? Pathology as practiced at the autopsy table has left many questions about diabetes unanswered. The use of the biopsy as applied to many other diseases has been largely neglected in the case of diabetes. The reasons for this are obvious. The pancreas is not readily available for biopsy and there are few situations in which a striking change in diabetes may take place. In the absence of gross disease, biopsy of the pancreas, when the organ is exposed at operation, is usually a simple and safe procedure. In experimental diabetes and in the rare instances of *diabetes associated with adrenal tumors one finds circumstances in which* the function of the islands may be tested in a striking manner. Sections of the pancreas preceding the production of experimental diabetes and sections from human biopsies will be examined in the light of what the remaining islands were able to do after the sections were taken.

Figure 1 A shows an island of Langerhans of a normal rat. This species is not made diabetic by growth hormone[1] but is quite susceptible to alloxan. The rat develops severe but temporary diabetes from large doses of corticotropin or cortisone.[2, 3] No matter how long the adrenal hormones are given, no matter how long the hormonal imbalance and hyperglycemia are continued, these islands do not develop hydropic degeneration.[4] They have considerable capacity for hyperplasia.[4, 5] When the administration of adrenal hormones is stopped and even when it is continued, the glycosuria disappears and the animal does not become permanently diabetic. The islands of the rat cannot hypertrophy enough to compensate for the gross destruction caused by alloxan or 95 per cent pancreatectomy, but even then the islands which remain appear to maintain their structure.

Figure 1 B illustrates the islands of a normal cat. Omitting technical details they will be described as essentially similar to those of the rat. The cat cannot be made diabetic with cortisone[6] and it is extremely resistant to alloxan.[2] However, partial pancreatectomy, or the administration of growth hormone,[7, 8] or massive injections of glucose[7] readily produce hyperglycemia. Under all of these conditions the islands, unlike those of

From the George S. Cox Medical Research Institute, University of Pennsylvania, Philadelphia.

TABLE 1

Responses of Two Species to Diabetogenic Procedures

Observation	Rat	Cat	
Diabetes from growth hormone	No	Yes [4]	Extra pancreatic
Diabetes from ACTH or cortisone	Yes [3]	No[4]	
Diabetes from alloxan	Yes[3]	No (?)[2]	Insular
β cells breakdown (hydropic etc)	No	Yes[2]	
Island hyperplasia	Marked [4]	Slight (?)	

What is known of the behavior of the islands of Langerhans in man? The lesions at autopsy have been studied and the insulin content and changes in granulation[3] have been described There is little knowledge of the islands in man in the earlier periods of the diabetic patient s life The *biopsies of three persons whose diabetes was associated with disorders of* the adrenal glands will illustrate the difficulty of correlating appearance and behavior of this organ in man

Figure 2 A illustrates the islands of a 43 year old woman whose history has been briefly reported [9] She had mild diabetes for one year and needed 15 units of insulin daily on a maintenance diet On this regimen she had a slightly elevated morning blood sugar usually about 160 mg per 100 ml *before her operation The operation was performed to remove a pheo-*chromocytoma which had caused typical symptoms for 5 years At operation the biopsy of the pancreas (Fig 2 A) showed marked degranulation or early hydropic degeneration of the beta cells After operation she recovered from her diabetes as indicated by an entirely normal glucose tolerance test 6 months after she left the hospital The point is that these are islands of a patient who recovered completely when the metabolic *stress of the medullary tumor was removed*

Figure 2 B is from the pancreas of H S a woman who also had diabetes and a pheochromocytoma She was 67 years old and diabetes had been diagnosed 4 years before this section was taken At first her diabetes was controlled by diet then insulin was needed when hyperthyroidism developed After treatment of this complication with radio-iodine insulin was stopped About one year before operation she began to have the symptoms of adrenal medullary hypersecretion which included paroxysmal hypertension and increasing glycosuria Shortly before operation treatment with insulin was resumed and 30 units daily were required to control the diabetes at that time At operation in December 1954 a medullary tumor of the left adrenal was removed and this section was taken This *operation was followed by relief of her symptoms* and a return of the blood pressure to normal Events which indicated that there were no multiple

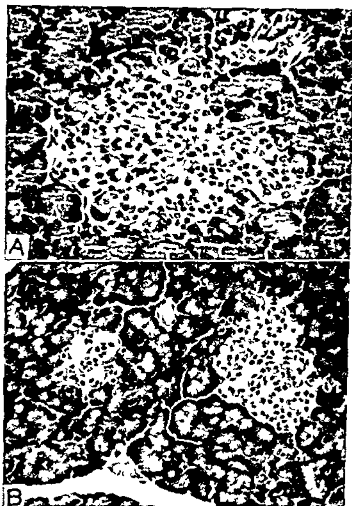


Fig. 1. Normal islands of Langerhans. A, rat. B, cat.

the rat undergo degranulation, hydropic degeneration and ultimately atrophy.[7] Permanent diabetes is the result.

Table 1 summarizes the differences in the behavior of these two species. The diabetogenic activity of growth hormone or corticotropin is largely if not entirely extra-pancreatic in nature. The difference between the activity *of these hormones in these animals probably has nothing to do* with the islands. On the other hand, the last three lines of Table 1 are direct responses of the island. The similarity of appearance and the marked differences in the behavior of the islands in these two animals should arouse the questions and the labors of laboratory investigators.



Fig 3 Patient A P A Hyaline degeneration of islet B Hyperplasia of islet

who had Cushing's syndrome for which bilateral adrenalectomy was performed The section of the pancreas was taken at the time of the second adrenalectomy Symptoms and findings of Cushing's syndrome developed rapidly in March 1955 and in May 1955 she was found to have diabetes for which she was given diet and 50 units of insulin daily In the University of Pennsylvania Hospital she was first controlled on a diet of protein 70 fat 70 and carbohydrate 140 gms and 60 units of insulin daily On June 26th the right adrenal was removed After this the dose of insulin was gradually reduced to 20 units daily even with slight fever This improve



Fig. 2. Islands of Langerhans.
A. Patient A. S. The pale cytoplasm indicates early hydropic degeneration. B. Patient H. S. These resemble normal islands.

or accessory tumors. Her diabetes improved so that she was managed without insulin but her glucose tolerance test was still grossly abnormal.

In summary, a mild diabetic whose disease was exaggerated once by hyperthyroidism and once by a pheochromocytoma was restored to her originally mild diabetic state by the removal of an adrenal tumor but was not cured like the first patient (A. S.). The islands of H. S. showed less morphological change than the islands of A. S. who recovered.

Figures 3 A and B show the pancreas of a 53 year old woman (A. P.)

diabetes There is no relation between the known duration or the severity of the diabetes before operation and its postoperative course In such patients one ought to distinguish between the improvement in diabetes and the so-called recovery from diabetes We have used the reduction in insulin requirement and the reversal to normal of the sugar tolerance test as criteria of these responses Such assumptions demand validation by the observation of many more patients for much longer periods of time

In the case of Cushing's syndrome Sprague et al[17] reported that Of the 10 patients who had frank diabetes before operation 7 had normal values for fasting blood sugar and no glycosuria after operation The operations were total or subtotal adrenal resection and sugar tolerance tests and other details are not available McCullagh and Alivisatos[18] cite two patients with Cushing's syndrome who had complete clinical recovery following adrenal surgery Apparently the same possibilities for improvement or recovery of diabetes apply to patients with adrenal cortical hyperfunction

Like man animals may show different behavior of the islands at different times After partial pancreatectomy or during treatment with pituitary extract in dogs and cats the islands undergo hydropic degeneration and atrophy but during the subsequent permanent phase of diabetes there may be no progression in the severity of the diabetes even though the hyperglycemia and glycosuria resemble the conditions of the causative period

Summary

Biopsies of the pancreas of three diabetic patients have been viewed with the subsequent course of the diabetes in mind After removal of a pheochromocytoma one patient recovered from diabetes another improved but did not recover (Recovery here refers to a return of the glucose tolerance test to normal limits) A third patient improved but still required insulin after total adrenalectomy for Cushing's syndrome These preliminary observations in man have been compared with those of experimental diabetes in an effort to relate the morphology of the islands to their functional capacity under various conditions

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ment is greater than one might expect from unilateral adrenalectomy and such a course often follows adequate insulin dosage of several weeks duration. In any case both factors were present.

On July 12th left adrenalectomy and pancreatic biopsy were performed. Post-operatively there was slight drainage from the wound which was attributed to the pancreatic biopsy. Her post-operative febrile reaction was less severe than usual but lasted for 2 weeks. She was discharged on the following regimen:—A diet of protein 100, fat 100, carbohydrate 260; 50 mgs. cortisone daily and 4 gms. enteric coated salt tablets; and 10 units of NPH insulin daily. For the last 5 days in the hospital she was free of glycosuria on this regimen.

The mixed histological appearance of Figure 3, A and B in one small sample of tissue is related to the following principal events:—(a) the reduction in insulin requirement by diet and insulin in a diabetic treated within 4 months of the diagnosis of the disease;[10] (b) the removal of one and later of both adrenals; (c) a final need for some insulin on a diet which the writers consider unduly large and a maintenance dose of cortisone. In view of the appearance of the islands, it is our opinion that cells which appear to be unlikely to improve (contrast Fig. 3) have been relieved of a large metabolic burden. The nondiabetic ought to tolerate the diet and dose of cortisone which she is taking so that she has not recovered in spite of this demonstrable improvement.

Discussion

Examination of a few of the reported cases of diabetes and pheochromocytoma (Table 2) shows that such persons may or may not recover from

TABLE 2

Variable Response of Diabetes after Removal of Pheochromocytoma

No.	Patient Reference	Duration of Diabetes (pre-op.)	Duration of Observation (post-op.)	Insulin Units		Glucose Tolerance (Post-op.)
				Pre-op.	Post-op.	
1	11	3 yrs	5 mo	15–25	0	Normal
2	12	7 mos	7 wks	10–15	0	Normal
3	13	11 mos		40–80	0	Normal
4	13		5 wks	0	0	See note
5	14		6 mos	0	0	Normal
6	V S	11 mos	6 mos	5–15	0	Normal
	15	3–4 mo	10 mos	8	0	Abnormal
8	16	?	10 yrs	?	?	See note
9	H S	4 yrs	8 mos	0–[illegible]0	0	Abnormal

Tolerance tests not reported in case 4; normal blood sugars and in case 8 an unchanged severity of diabetes postoperatively.

ANTERIOR PITUITARY INSUFFICIENCY: A STUDY OF 18 CASES

By H. St. George Tucker, Jr., M.D., and (*by invitation*) Frank A. Wade, M.D., and Isabel Taliaferro, M.D.

Richmond, Va.

Anterior pituitary insufficiency in the adult has been well described by many recent authors.[1-12] It is clear that the clinical picture is largely that of variable combinations of thyrotropic, gonadotropic and adrenocorticotropic hormone deficiencies with resultant failure of the corresponding target glands. Potent oral or buccal replacement therapy for each of these target glands is now available. Successful management of these patients is quite feasible, but requires careful evaluation of the various glandular failures present in each case. We have for some time been interested in the pattern of glandular failure in pituitary disease and in the estimation of the various deficiencies present. In this paper we will present observations made on eighteen such patients.

Material

The eighteen patients were seen in the Medical College of Virginia Hospitals or in the McGuire Veterans Administration Hospital. They consist of seven cases of postpartum pituitary necrosis and eleven cases of pituitary tumor (ten chromophobe adenomas and one chromophobe carcinoma). The relative number of cases of each type is of no significance for various reasons, most obviously because the population of the Veterans Hospital is predominantly male and furnished only cases due to pituitary tumor. All the postpartum cases gave a typical history of onset of symptoms following severe hemorrhage or shock at the time of childbirth. Six of the pituitary tumors were verified at operation (cases 1, 4, 5, 6, 8, 11) and two at autopsy (cases 3, 7). In all cases there was unequivocal evidence of enlargement of the sella turcica on roentgenogram of the skull or of visual field constriction of a type to indicate chiasmal pressure. We omitted from this study certain other cases of apparent pituitary insufficiency of unknown cause, since we could not exclude the possibility of hypothalamic damage as the primary cause rather than a lesion in the pituitary gland.

Observations and Discussion

Most of the pertinent data are recorded in Table I. Various other observations made in certain cases will be referred to separately in the text.

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DISCUSSION

Dr Howard F Root (Brookline Mass) Dr Lukens presentation is most interesting We have just had a patient with a large pheochromocytoma which surrounded the aorta and was finally removed together with one kidney and the spleen That patient required a good deal of insulin during the months preceding diagnosis and operation because of hyperglycemia and glycosuria Yet now a few months since the operation he no longer requires insulin and blood sugar values are normal Perhaps a 5 year period of observation would be necessary before a final statement that the diabetic state has been cured is justified This raises the question of whether true diabetes mellitus exists without the hereditary background Certainly Dr Lukens report stimulates all of us who see diabetic patients with other glandular complications to make use of an opportunity to secure biopsies of the pancreas

9 J W B	M 30	Chro phob d 3 yrs	++	+++	++	t go J t pa Loss 40 lbs	−14	198	3	124 4 0	7 2-9 7		9 → 14 4	(3)	N 1	Ios 8 N g 13
10 C P	M 6	Cl pla be d m) yrs	+++	1	0	H dach Loss G 50 lb	−70		62 42	111/4 3	2 2				N 1	N g 6
11 A D	F 5	Cl m phobe d 3 yrs	++	++++	++	Ls l loss H d)	−31	515		140 5 6	6-4 7	0 4	4 7 → 0 3	(1)	N 1	N g 6
1 G L	F 9	Postpart ecro 9 yrs	++++	++++	1	G n 30 lb	−1	310	11	136 4 2	0 8-1 4	0 33	1 1 → 5 1	(4)	N 1 (ITT 1 m 1)	I os 3 N g 6
13 P L	F 59	Postpart ecros 30 y	+++	+++	++++	Act t be 1 is Loss 30 lb	−36	2 5		11 3 6	0 1 1 0	0 1	0 1 → 5 1	(3)	N m 1	Pos 8 N g 13
14 M B	F 35	Postpart ecros 18 yrs	+++	++++	1	Wt gu	−32	590	27	140 4 0	0 5-2 6	0 05			N n 1	Pos 3 N g 8
15 O H	F 56	Postp t m necrosis 20 yrs	++++	+++	++++	1 ss 20 lbs	−24	330	10	110 4 0	1 5-3 3	0 39	2 0 → 0 9	(2)	0 1	N g 6
16 A C	F 39	I tpart m ecrosis 8 yrs	++++	+++	++++		−21	18	1	135 4 6	1 0-2 1	0 36	2 2 → 4 3	(3)	21	N g 3
1 F M C	F 45	Postp tu necros 8 yrs	++++	+++	++++		−30	19	20	1 4 4 7	0 0-2 0	0 46	2 0 → 5 5	(5)	5[f]	N g 6
18 H F	F 36	Postpart ecros 14	+	+++	+++	Ch t ray t f Th	−3	3 4	5	117 3 8	0 5-0		0 6 → 1 3	(4)[d]	3	I 13 ± 52

ACTH sch d 1 5 U S P t d y t y 8 ho 1 I d 1
[b] ACTH 1 d 1 5 U S P t f M q 6 hr
ACTH sel ed 1 5 U S I ta I M t 10 t q 6 hrs
[d] ACTH sel ed 1 20 U S P un ts ACTH g I I M q 12 hrs
Th b mality Ins l n T l ra ce Test cons ted f n ld hypogl re m respo nse
[f] Spont neou ly pe rr g hypogl cemia t1 coma

TABLE I

Summary of Data on I atients With Interior Pituitary Insufficiency

Case No.	Se Ag	D g D t	Cl cal Cla d 1 D fi ncy			Other Symptoms	B M R	S um Ch le terol	Wate T t I d A=	Serum N /K	Ur nary 17 K to- stero d	Urinary Fo m lde hyd gen c Corti os te d	17KS Re po se to ACTH			Bl od ug r fte 18 24 hrs fasting	FSH
			G d	Thy d	Ad								B f r ACTH	Aft ACTH	( ) D y on ACTH		
							%	mg %		meq/l	mg / 24 h	mg / 24 h	mg / 24h	mg / 24h		mg %	mo / 24 h
1 E S	M 35	Chromophobe 1 3 yrs	++++	+++	++	V 1 los	− 2		15	N m l	1 0					N mal	Pos 6 N g 13
2 C 1	M 29	Chro p1 be d 6	++++	++++	++++	H d cl S d t t mpt	−3	195	2	N l	1 0-2 0	0 0	1 6	→ 3 1	(3)	57 69	N g 6
3 J W	M 48	Chr phobe 1 4 rs	++++	+++	+++	H d ch J t pa s Los 15 lb	− 6	340	6	1 6 5 9	1 6– 2	0 18				N m l (ITT b n m l)	N g 3
4 C W	M 36	Chromophobe 1 4 rs	++++	+++	1	V al l ss	−27	262	8	136 5 2	2 4 3 1	0 12	4 8	→ 9 2	(3)	No mal (ITT r m l)	N g 3
5 H J	M 34	Chr p1 be 1 2 rs	+++	++	1	V l loss	−28	252	2	135 5 5	3 5	0 52				N mal (ITT no mal)	I 6 N g 13
6 E C	M 39	Chro p1 be 1 no s 6 mos	+++	++	1	D betes ns p d Headach Vis l loss	−33	1 5	9	144 5 3	3 6–7 2	0 23	4 1	→ 14 5	(4)[b]	N m l	N g 3
J H	M 56	Chr p1 be 1 nom 2 rs	++++	++	+	Ad ced t be u los Em t n		80	5	128 3 7	0 9–1 7	0 0				N n l	
8 I	M ??	Chr op1 be car no na 2 yrs	+++	+++	++	Diabetes ns p d Head h Vis l loss St po	−41	415	2	174 5 2	2 0	0 21	2 0	→ 4 0	(4)	N m l	N g 6

9 J W W	M 50	Chr[illegible] [illegible]	++	+++	++	[illegible] 1 wa 40 lbs	−11	109	3	121 4 0	7 2 9 7		9 → 11 4	(2)	N 1	Pos 6 N ≥ 13
10 G P	M 62	Chr[illegible]	+++	1	0	Read 1 [illegible] n 30 ft	−20		62 42	111 4 2	3 2				N 1	N ≥ 8
11 A D	F 3	Chr[illegible]	++	++++	++	[illegible]	−31	515		110 5 5	2 3 4	0 4	4 → 0 3	(7)	N 1	N 6
12 C L	F [illegible]	Po[illegible]part [illegible]	++++	++++	?	1 n 30 lbs	−1	210	11	136 4 2	0 8 1 4	0 37	1 1 → 5 1	(1)	N 1 (1T1 1 n 1)	1 m 3 N ≥ 6
13 E L	F 50	[illegible]partum [illegible] 30	+++	+++	++++	N 1 1 be [illegible] 1 wa 30 lbs	−30	223		112 3 6	0 1 1 0	0 22	0 1 → 3 4	(7)	N 1	P u 6 N ≥ 13
14 M B	F 35	Postpart [illegible]	+++	++++	1	[illegible]	−32	540	2	110 4 0	0 6 2 6	0 05			N 1	1 m 2 N ≥ 6
15 O H	F 38	P[illegible]	++++	+++	++++	1 m 90 ll	−21	370	10	110 4 0	1 5 3 3	0 28	2 0 → 0 9	(2)	0 1	N ≥ 6
16 [illegible]	F 30	Post[illegible]	++++	+++	++++		−4	13	1	138 1 8	1 0 2 1	0 36	2 2 → 4 3	(5)	21[f]	N ≥ 3
[illegible] I M C	F 45	Post[illegible]	++++	+++	++++		−30	152	90	1 9 4 7	0 9 2 0	0 16	2 0 → 8 3	(6)	5[f]	N ≥ 8
18 H F	F 30	Postpart[illegible]	+	+++	+++	Chr[illegible] f The	−31	3 4	5	11 3 8	0 3 0		0 6 → 1 3	(1)[d]	2	1 m 13 ± 32

ACTH [illegible] 5 U S [illegible] unit [illegible] 8 [illegible]
ACTH [illegible] 5 U S P unit I M [illegible] 8 hrs
ACTH [illegible] 5 U S P unit I M [illegible] 10 [illegible] 8 hrs
[illegible] ACTH [illegible] 20 U S P [illegible] ACTH [illegible] I M q 12 hrs
Th[illegible] mality Insul[illegible] T[illegible] [illegible] [illegible] glucose [illegible]
[illegible] hypoglycemia [illegible]

Clinical Picture

The clinical picture of pituitary insufficiency is seen in its most typical form in the cases of postpartum necrosis where symptoms due to pressure on surrounding structures do not complicate the picture The history in cases 12 through 18 is that of good health until the occurrence of severe hemorrhage at the time of childbirth This is followed by failure of lactation and persistent weakness leading to a state of chronic poor health Symptoms include lassitude apathy coldness dryness of the skin loss of libido and falling out of axillary and pubic hair or failure of shaved pubic hair to regrow Complete and permanent amenorrhea is the rule although some patients may continue irregular menstruation for a year or so (cases 13 14) and one of our patients (case 18) was still menstruating irregularly after 14 years These patients never really feel well from the time of hemorrhage but their apathy is such that they seldom volunteer complaints and are usually brought to the physician by relatives

The appearance of these patients is strikingly similar Their expression is dull and lifeless and often typical of myxedema Where frank myxedema *is lacking other features of hypothyroidism are seen such as lateral thinning* of the eyebrows dryness and pallor of the skin and often a fine wrinkling that may give a prematurely aged appearance The pallor is out of proportion to the moderate anemia present and is due also to the lack of capillary circulation in the skin and to a decrease in the melanin pigment present The dry pallid skin has been aptly described as having a ground glass or alabaster appearance Axillary hair is universally absent and pubic hair is either absent or markedly thinned The breasts often appear full but on palpation contain little glandular tissue The genitalia show atrophic changes and the uterus is small Weight loss is not a prominent feature and most of our patients appeared plump or at least of normal weight

Where pituitary insufficiency is caused by tumor (cases 1–11) symptoms due to pressure *on adjacent structures are likely to bring the patient to* medical attention before the glandular deficiencies become extreme Visual disturbance was a presenting symptom in three cases diabetes insipidus in two and headaches were a prominent complaint in six of the eleven tumor patients When glandular deficiencies develop the findings are much as described above In males loss of libido and potency is an early symptom accompanied by progressive loss of beard and of all body hair as well as of axillary and pubic hair The external genitalia may appear unchanged but the testes are usually soft and atrophic

Because of the progressive growth of the pituitary tumors and also because of the pressure symptoms produced these patients are discovered much earlier than those with the static pituitary damage following post

partum necrosis The average duration of symptoms in the tumor cases was $3\frac{1}{2}$ years that of the postpartum cases 1.5 years

Glandular Interrelationship

In any attempt to evaluate the degree of failure of the thyroid gonad and adrenals in pituitary insufficiency one must consider possible interrelationships of glandular failure It is well known that hypothyroidism can produce impairment of gonadal and adrenal function In some of our cases treated initially with thyroid alone it was possible to compare studies before and after thyroid In five cases where the Kepler Robinson Power water test[14] was positive initially there was no significant change after thyroid Urinary 17 ketosteroid was measured before and after the administration of thyroid alone in six patients In four women with 17 ketosteroid values below 2 mg per 24 hours (cases 12 13 14 16) there was no significant rise in the figure when the patient was receiving full doses of thyroid Two males (cases 4 and 6) with somewhat higher initial levels of 17 ketosteroid showed a slight rise after thyroid In seven patients the follicle stimulating hormone (FSH) titre in the urine was equally low before and after thyroid These observations are of little significance except to indicate that in these patients the gonadal and adrenal insufficiency was independent of the effects of hypothyroidism

Specific Glandular Deficiencies

We undertook to evaluate the degree of gonadal thyroid and adrenal failure in each patient purely on the clinical evidence then correlated this with the results of various laboratory tests These observations are listed in Table I but the following comments can be made

1 *Gonadal Deficiency* Gonadal deficiency has been regarded by some as the first deficiency to result from pituitary damage and as the *sine qua non* of the syndrome Gonadal deficiency was quite advanced in all but three of our patients but these three are notable Patient 9 a man with a pituitary tumor had had definite hypothyroidism for 3 years and had enough adrenal deficiency to produce hyponatremia but impotence was the only evidence of gonadal deficiency He showed normal axillary and pubic hair and some chest hair normal genitalia and had 17 ketosteroid and FSH determinations within the normal range Patient 11 a 52 year old woman with a chromophobe adenoma of the pituitary had had amenorrhea for 3 years but continued to have menopausal hot flushes for 2 years after the development of hypothyroidism Since gonadotropic deficiency in women is not associated with hot flushes it is suggested that in this patient gonadotropic deficiency did not develop until after the thyroid deficiency The most striking example of continuing gonadal function was patient 18

who continued to menstruate 3 or 4 times a year for 14 years after a near fatal postpartum hemorrhage which *resulted in severe thyroid and adrenocortical deficiency*.

2. *Thyroid Deficiency.* There was definite clinical evidence of thyroid deficiency in all but one patient. Case 10, a 68 year old male with pituitary tumor, had had almost complete hypogonadism for 15 years without any clinical or laboratory evidence of thyroid or adrenal deficiency. The others all showed hypothyroidism of varying degree. Most of these patients were seen before I^{131} uptake and serum protein bound iodine determinations were available and therefore the clinical estimation of their hypothyroidism is probably more reliable than the laboratory procedures reported. For various reasons the basal metabolic rate is not a good index of thyroid insufficiency in pituitary failure. It is well known that the metabolic rate is low in adrenal deficiency and it has also been shown that it may be low in gonadal insufficiency.[15, 16] In most of our cases the basal metabolic rates were quite low, but they did not correlate well with the degree of clinical hypothyroidism and tended to remain low after adequate doses of thyroid had been given. Also, as reported by all observers, the serum cholesterol was quite variable, being elevated in about half our patients with thyroid deficiency and normal in about half. The serum protein bound iodine and I^{131} uptake are much better indices of thyroid deficiency. These tests were done with the more recent patients in this series and correlated quite well with the clinical estimate of thyroid deficiency.

An increase in thyroid function following the administration of thyroid stimulating hormone (TSH) has been generally considered characteristic of pituitary myxedema as opposed to primary myxedema.[17, 18, 19] Querido and Stanbury[19] suggested that in some cases of long standing pituitary failure the thyroid gland might become fibrotic and unresponsive to exogenous TSH and described one such case, but little mention of this has been made in other reports. We have seen such a lack of response to TSH in two patients with pituitary myxedema, one case 18, and the other a male patient not included in this series because the nature of his pituitary damage was not determined. Figure 1 illustrates the difference in I^{131} uptake in two patients with very similar pictures of postpartum pituitary necrosis. Case 17 with a lesion of 8 years' duration showed a good rise in I^{131} uptake and also in serum protein bound iodine after receiving 10 U.S.P. units (25 mg.) of TSH daily for 3 days, while case 18 with a lesion of 14 years' duration showed almost no rise with the same amount of TSH. It is likely that a longer period of TSH administration would ultimately stimulate thyroid function in all cases, but the possibilities of such variations in response must be understood if any standard period of TSH stimulation is to be used as a test.

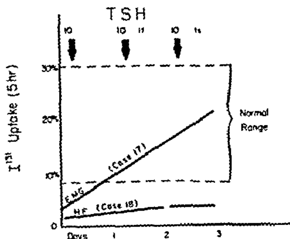


FIG 1 Illustrates the difference in 5 hr I^{131} uptake response to TSH stimulation of two very similar patients with postpartum pituitary necrosis It can be presumed that the thyroid gland of case 18 had undergone considerably more atrophy than that of case 17

3 *Adrenocortical Deficiency* Deficiency of the adrenal cortices is much more difficult to judge clinically than are gonadal and thyroid insufficiency Seven of our patients showed obvious adrenocortical deficiency with *crises hypoglycemia or severe hyponatremia (cases 2 3 13 15 16 17 18)* Five showed lesser degrees of deficiency usually evident only under stress (cases 1 7 8 9 11) Six were judged to have little or no adrenal deficiency clinically (cases 4 5 6 10 12 14) However laboratory studies indicated that many of the latter had very significant impairment of adrenocortical *reserve The Robinson Kepler Power water test was positive in 14 of 16* cases tested Urinary 17 ketosteroid was definitely low in all cases except patient 9 who had moderately impaired adrenal function but only minimal evidence of gonadal deficiency Urinary formaldehydogenic corticosteroids were sometimes low but often in the normal range even where definite *adrenocortical insufficiency was present This test is not a sensitive index* of adrenal insufficiency

The effects of ACTH stimulation on 17 ketosteroid excretion were variable Some of the results are illustrated in Fig 2 It can be seen that while some patients show a prompt rise in 17 ketosteroid excretion follow

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unnecessary for routine use. Observation of the effect of prolonged fasting on the blood sugar is not a very sensitive index of adrenal impairment but will serve to detect any severe disturbance in carbohydrate metabolism.

Definite hyponatremia was found in seven patients (cases 3, 7, 9, 13, 15, 17, 18). Low serum sodium and chloride values have been repeatedly noted in hypopituitarism by all observers, but the finding is of considerable interest in view of the growing body of evidence recently summarized by Gaunt *et al*[22] that the adrenal secretion of aldosterone or other sodium retaining factors is not under the complete and direct control of ACTH. Farrell *et al*[23] have shown that hypophysectomized dogs continue to secrete aldosterone at about two-thirds the normal rate. Where surgical hypophysectomies have been performed in human beings, supportive cortisone has always been given so that it is difficult to know how much tendency there is to lose salt. Maclean *et al*[24] have shown that hypophysectomized patients retain salt much better than adrenalectomized patients on the same dose of cortisone and conclude that the pituitary is not necessary for the adrenal regulation of salt balance. Why then do these patients with long standing pituitary insufficiency develop hyponatremia? The answer must lie in the degree of atrophy of the adrenal glands that has occurred. If the regulation of electrolyte balance is an autonomous function of the adrenal cortex, it may be unaffected in the early post-operative period following hypophysectomy while the adrenal cortices remain fairly intact but lost at a much later date when the adrenal cortices have become atrophied. This implies a dissociation between the pituitary adrenocorticotropic factor necessary for the support of adrenocortical cells and some other unknown factor which causes the same cells to secrete more or less aldosterone. The autopsied cases of severe hypopituitarism reviewed by Sheehan and Summers[4] almost all showed such marked atrophy of the adrenal cells that it would appear likely that any function of these cells, autonomous or otherwise, would necessarily be impaired. Two of our patients who had had hyponatremia subsequently came to autopsy. Case 3 showed very severe atrophy of the adrenal cortices. In case 7 the adrenals showed atrophy but not as marked. This patient died of pulmonary tuberculosis after a long wasting illness. It is likely that the stress of his prolonged illness was an additional factor contributing to the hyponatremia without such complete atrophy of the adrenal cortices.

The Pattern of Glandular Failure

At this point we may summarize the glandular status of our cases as follows. Most of the eighteen patients showed definite evidence of both gonadal and thyroid deficiency. No definite evidence was found that either

Effects of ACTH on 17KS Excretion in Anterior Pituitary Insufficiency

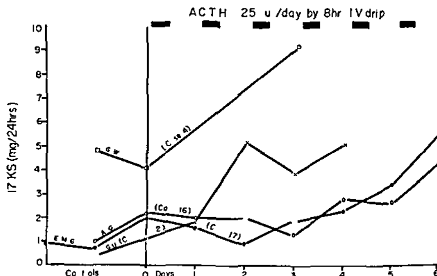


FIG 2 Illustrates different types of response of urinary 17 ketosteroid to ACTH in patients with anterior pituitary insufficiency

ing ACTH others may require ACTH administration for five or six days or longer before any significant 17 ketosteroid response is seen These results undoubtedly reflect varying degrees of atrophy of the adrenal cortices Knowlton et al[10] called attention to this delayed and subnormal response of the adrenals to ACTH in cases of hypopituitarism of long standing It should be noted however that in some patients the adrenal cortices may be responding to ACTH even though there is no rise in 17 ketosteroid excretion Patient 1a became euphoric and psychotic after 2 days of ACTH although 17 ketosteroid rose only slightly and patient 18 showed marked improvement during 4 days on ACTH with only a negligible rise in 17 ketosteroid excretion This may reflect qualitative differences in the steroids that the long atrophied adrenal can produce as well as a lack of sensitiveness of the 17 ketosteroid output as a measure of adrenocortical activity

Severe hypoglycemia occurred in only two patients (cases 16 and 17) both of whom had spontaneous hypoglycemic coma In the other patient blood sugars were seldom significantly low even after 18 to 24 hours fasting In some cases without hypoglycemia on fasting insulin tolerance tests[1] showed varying degrees of hypoglycemia unresponsiveness but the test adds little to the evaluation of the patient and was considered

6 the administration of ACTH brought about a definite return of the polyuria (Fig 3) It appears that the presence of the adrenocortical diuretic factor is necessary for the maintenance of diabetes insipidus and that its loss causes the disappearance of polyuria when the anterior pituitary fails The critical condition of case 8 permitted only fragmentary observations on the diabetes insipidus - adrenal relationship His previous severe polyuria had subsided to an output of only about 1 litre daily when we saw him but he had become very lethargic and almost blind There was no return of polyuria during ACTH administration but the very slight rise in 17 ketosteroid excretion suggested that the adrenals were not capable of responding adequately to ACTH stimulation When oral cortisone acetate 50 mg daily was given the urine output rose to 3 litres daily The urgent necessity for surgery cut short these observations At operation a large chromophobe carcinoma of the pituitary was found which could only partially be removed Post operatively a maintenance dose of cortisone 12 5 mg daily did not cause return of polyuria We hoped to observe the effect of various doses of cortisone and of other steroids on the urine output but the patient's rapid deterioration prevented any further reliable observations

Treatment and Results

Treatment has consisted of substitution therapy at the target gland level with thyroid testosterone and cortisone At first we gave cortisone only to patients with obvious adrenal deficiency but we now believe that it should be given to all patients with any impairment of adrenal reserve Cortisone acetate is given orally in the least dose that produces a state of reasonable well being usually 10 mg to 20 mg daily given in divided doses every 6 hours or every 12 hours When any stressful situation arises the cortisone dose must of course be raised many fold usually to 100 or 200 mg daily If nausea or vomiting occurs intramuscular cortisone acetate or intravenous hydrocortisone should be given Deoxycorticosterone acetate was given to most of the earlier patients but since cortisone has been used DCA has not been necessary Occasionally a small supplement of salt is added to the diet

Desiccated thyroid should be started in very small dose of 15 mg to 20 mg daily and the dose very gradually increased allowing at least a month at each dose level before increasing If there is any suggestion of *adrenal insufficiency cortisone should be given before thyroid is begun* We have seen at least one patient (case 16) where the administration of thyroid without cortisone precipitated a crisis of acute adrenal insufficiency The final dose of desiccated thyroid given to our patients has varied from 60 mg to 180 mg daily

Most of the men and some of the women have been given testosterone

gonadotropic or thyrotropic hormone is lost first. One case showed severe gonadal deficiency without any loss of thyroid function and several showed retention of at least some gonadal function for a long time after thyroid deficiency was well established. It is clear that adrenocorticotropic hormone is the last to be lost as the pituitary fails. However subclinical states of impaired adrenocortical reserve may be present long before adrenal insufficiency becomes evident.

Diabetes Insipidus and Adrenal Function

Diabetes insipidus was a presenting symptom in two patients with pituitary tumors (cases 6 and 8). It is of interest that the polyuria diminished as the symptoms of anterior pituitary insufficiency developed, ultimately disappearing in both patients. This phenomenon has been observed by others[5] and is in keeping with the concept that an intact anterior lobe is necessary for the occurrence of diabetes insipidus. In case

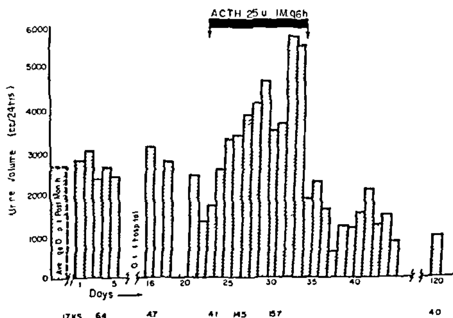


Fig. 3. Patient P. G. had developed diabetes insipidus as the first sign of her pituitary tumor. As anterior pituitary insufficiency developed the polyuria had diminished from 7000 cc. or more to 3000 cc. daily. This chart illustrates the increase in urine output produced by ACTH stimulation of the adrenal. The rise in urinary 17 ketosteroid during ACTH administration is also shown.

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gonadotropic or thyrotropic hormone is lost first One case showed severe gonadal deficiency without any loss of thyroid function and several showed retention of at least some gonadal function for a long time after thyroid deficiency was well established It is clear that adrenocorticotropic hormone is the last to be lost as the pituitary fails However subclinical states of impaired adrenocortical reserve may be present long before adrenal insufficiency becomes evident

Diabetes Insipidus and Adrenal Function

Diabetes insipidus was a presenting symptom in two patients with pituitary tumors (cases 6 and 8) It is of interest that the polyuria diminished as the symptoms of anterior pituitary insufficiency developed ultimately disappearing in both patients This phenomenon has been observed by others[5] and is in keeping with the concept that an intact anterior lobe is necessary for the occurrence of diabetes insipidus In case

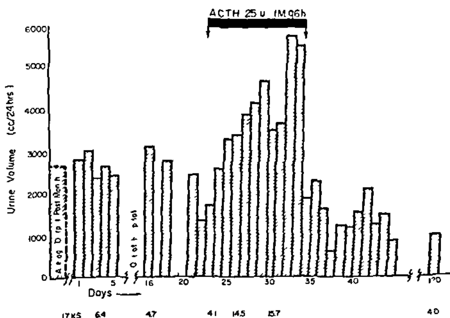


Fig 3 Patient P G had developed diabetes insipidus as the first sign of his pituitary tumor As anterior pituitary insufficiency developed the polyuria had diminished from 7000 cc or more to 3000 cc daily This chart illustrates the increase in urine output produced by ACTH stimulation of the adrenals The rise in urinary 17 ketosteroid during ACTH administration is also shown

Summary and Conclusions

1 A study of eighteen patients with anterior pituitary insufficiency has been presented The clinical features have been reviewed and the glandular failures present in each case have been analyzed

2 Both gonadal and thyroid function are impaired early in pituitary insufficiency and it cannot be said from this study that either is necessarily lost before the other Adrenocortical function is the last to be impaired as the pituitary progressively fails

3 There is considerable variation in the degree of atrophy of the various target glands and this is reflected in variable responses to stimulation tests with trophic hormones

4 Hyponatremia is a frequent finding in severe long standing pituitary failure Since the regulation of electrolyte balance by the adrenal cortex is thought to be independent of the pituitary the occurrence of hyponatremia in these patients suggests a considerable degree of atrophy of the adrenal cortices

5 If adrenocortical deficiency develops in a patient with diabetes insipidus the polyuria diminishes and eventually disappears but can be restored by giving ACTH or cortisone

6 Treatment of these patients with thyroid testosterone and cortisone is quite successful and will restore most of them to reasonably good health and activity

Acknowledgment

We gratefully acknowledge the technical assistance of Mr David W Miller M.S Biochemist McGuire Veterans Hospital for the special studies done on patients from that institution which are included in this report

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as either oral or buccal tablets, or as intramuscular injections of a slowly absorbable preparation. The dosage given to the female patients had usually been about one third that given as substitution treatment to the men. In both men and women testosterone has seemed to increase strength as well as to restore libido and potency in the males. Estrogens have been given to some of the women but often caused undesirable bleeding and seemed to add little to their over all welfare. The use of estrogens has been largely dispensed with in our patients.

Various problems may arise. Patient 3 was found to have old rheumatic heart disease with mitral stenosis. Even a small amount of cortisone produced heart failure and adrenal replacement had to be omitted in spite of fairly severe deficiency. He was maintained on thyroid and testosterone for six years but eventually died of heart failure.

Patient 2 developed a duodenal ulcer while receiving cortisone 25 mg daily. Even with cortisone reduced to 10 mg daily and in spite of every medical regimen the ulcer resisted healing. Ultimately subtotal gastrectomy was done under supportive cortisone and the patient has subsequently gotten along well on cortisone 10 mg daily.

Tuberculosis is a frequent complication in these chronically debilitated patients. This naturally complicates the question of cortisone treatment. We have felt that cortisone can be given in low dosage if needed but have also given isoniazide and para amino salicylic acid even where the tuberculous lesion appeared inactive. Two of our patients, 7 and 13, had advanced tuberculosis at the time pituitary insufficiency was diagnosed. In spite of vigorous chemotherapy both patients ultimately died of progression of the tuberculosis. Patient 7 received no cortisone and patient 13 received at the most 10 mg intramuscularly every other day.

The patients with pituitary tumors all received irradiation. This usually helped their vision but produced little change in their glandular status. In six cases surgical removal of the tumor was undertaken because of rapidly failing vision. With supportive cortisone the operations were well tolerated. *No improvement in glandular status was noted following* operation but neither was there any evidence the pituitary insufficiency had been made any worse.

The over all results of treatment have been gratifying. Of the 18 patients 4 have died, two of tuberculosis, one of heart failure and one of extension of pituitary carcinoma into the brain. The remaining 14 have been restored to reasonably good health for periods now up to eight years. Many of them have returned to their former occupations or to moderate housekeeping duties. They all regard themselves as markedly improved by treatment.

Summary and Conclusions

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DISCUSSION

DR JOHN T KING (Baltimore) *I would like to ask Dr Tucker a question concerning terminology* Are the cases to which you refer to be considered instances of Simmonds disease the so-called pituitary cachexia or are you describing a different entity?

DR WILLIAM B BEAN (Iowa City) Doctor Tucker has given us a very eloquent presentation I would like to stress the tremendous importance of recognizing the entire entity of anterior pituitary deficiency We must not think of myxedema only and treat just that because people so treated occasionally go into unexpected and even unrecognized Addisonian crisis

I would like to ask Dr Tucker if he has any notion why these patients who have sometimes as much adrenocortical inadequacy as a person with Addison s disease are completely depigmented whereas those with Addison s disease are pigmented This implies that an intact pituitary is needed but can be take it any further than that?

DR FRANCIS D W LUKENS (Philadelphia) Have the patients with diabetes insipidus whose polyuria became milder and then reappeared when they were treated with ACTH greatly increased their food intake Experimentally hypophysectomized animals have had their polyuria increased by forced feeding How does that agree with your patients?

DR EDWARD ROSE (Wynnewood) The idea that diabetes insipidus tends to be ameliorated pari passu with progressive insufficiency of the anterior pituitary is pretty well rooted but I am sure that occasionally both diabetes insipidus and anterior lobe deficiencies can coexist in the same patient

I have seen one patient with classic Sheehan s syndrome whose presenting complaints several months later were those of diabetes insipidus *One may only guess* that perhaps the vascular changes producing ischemic necrosis of the anterior pituitary also involved the neurohypophyseal region

DR C SIDNEY BURWELL (Boston) Is the frequency of this association of pituitary insufficiency with postpartum hemorrhage due to the fact that this is a very common cause of severe hemorrhage or is there something about the special state of the pituitary at the end of pregnancy which makes it vulnerable at this time?

DR WILLIAM McNEAL NICHOLSON (Durham) I enjoyed Dr Tucker s presentation very much but I was a little surprised and disappointed in his results in relation to the thyroidal uptake of I[131] after the injection of TSH In all but one of ten patients that we have studied we have obtained a distinct and satisfactory increase in the thyroidal uptake of I after giving TSH whereas in primary myxedema there was no response or increase in the uptake of I

The technique used by us is as follows 10 microcuries of I[131] was administered by mouth Twenty four hours later a count was made over the thyroid gland Immediately following this 10 units of TSH was injected and in twenty four hours the dose of I[131] was repeated *and again twenty four hours after this second dose* a repeat of the count was made

In comparing this technique with the three hour test we have found it to be somewhat more accurate and it has proven to be of greater aid to us In fact we believe that this test is one of the most valuable aids in the differentiation between *primary* myxedema and secondary myxedema due to anterior pituitary dysfunction I wonder if Dr Tucker has used this particular technique in the study of his patients

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ELECTROLYTES, WATER AND NITROGEN DISTRIBUTION IN MUCOSA AND MUSCULARIS OF HUMAN STOMACH AND COLON

By LAY MARTIN, M.D.

BALTIMORE

Introduction

In a previous report[1] the concentrations of potassium in human gastric juice before and at intervals after histamine stimulation were described. It was noted that during histamine stimulation of gastric secretion potassium varied directly with increasing concentrations of hydrochloric acid and inversely with sodium and nitrogen. It was suggested that the more elevated concentration of potassium during histamine stimulated hydrochloric acid secretion may be a function of parietal gland activity.

It seemed of interest to determine the concentration of these and other electrolytes in the mucosa and muscularis of the stomach and colon of man in hope that such data might lead to more basic interpretations of physiology of gastric secretion.

As the probability of obtaining tissues from normal human stomachs is less than rare and the opportunity of obtaining them from patients operated upon for peptic ulcer in a large hospital is good, such tissues were selected for analyses. The gastric mucosa and muscularis of patients with duodenal ulcers are frequently considered as normal on histologic examination and the segments of colons proximal to areas of carcinomatous degeneration are often reported as normal by pathologists.

The present study undertakes the analyses of mucosa and muscularis of human stomach and colon with respect to water, nitrogen, phosphorus, chloride, sodium, calcium and magnesium, for which no reports have been found in the literature. Reports of similar analyses in animal are scarce and incomplete. They have been well summarized in Mannery's admirable review. Those made in stomach mucosa of rat and rabbit[3,4] differ and those of the dog[5] resemble the values here presented. Previous estimations of calcium and magnesium in mucosal gastro-intestinal tissues were not found in a study of the literature.[2] Several analyses of smooth muscle have been reported in different animals,[9,10,11,12] those referring to the resting rat uterus[9] most closely approximating data in this report.

The specimens for analysis were obtained during operations on

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With technical assistance of Dorothy Wagner and Harry [illegible]berg.

The expenses of this investigation were defrayed by The Vernon Taylor Fund.

DR HENRY M THOMAS JR (Baltimore) Dr Tucker I would like to ask simply how large a dose of thyroxin did you give without obtaining any change in the basal metabolic rate and did you produce any evidence of *hyperthyroidism in this work?*

DR H ST GEORGE TUCKER JR (Closing) Dr King the matter of terminology has caused much discussion We use the terms postpartum necrosis of the pituitary and Sheehan s syndrome interchangeably to refer to those cases which follow hemorrhage or shock at childbirth Sheehan s syndrome is one particular type of Simmonds disease We do not like the term Simmonds cachexia because most of the patients are not cachectic

Dr Bean we do not have any new answer to the matter of pigmentation We have attributed the pigmentation of Addison s disease to the excessive production of melanocyte stimulating hormone by the pituitary and have thought that the lack of pigmentation in pituitary insufficiency is due to lack of this hormone The melanocyte stimulating hormone or MSH closely parallels ACTH We have seen pigmentation develop in patients receiving ACTH and have seen our Cushing s patients become more deeply pigmented after subtotal adrenalectomy when ACTH would be increased The giving of cortisone to the Addisonian patient seems to lessen the pigmentation Everything that we have observed seems to fit with the theory of pituitary melanocyte stimulating hormone as the cause of the pigmentation

Dr Lukens about the food intake during the administration of ACTH while I have no exact figures I think it is fairly safe to say that these patients did eat more Certainly they felt better and I feel sure that their food intake was increased

I was interested in Dr Rose s remarks about the patients with postpartum pituitary necrosis who developed diabetes insipidus We have not seen this It must not occur very often Certainly it is much more common in the tumor cases where there *is the additional factor of pressure on hypothalamic nerve tracts*

I would not want to say that diabetes insipidus cannot occur in the presence of anterior pituitary insufficiency but from our two cases and from other similar cases in the literature the anterior pituitary deficiency seems to make the diabetes insipidus much less severe

Dr Burwell asked about the state of the pituitary gland in women at the end of pregnancy and as to why the gland is more vulnerable at this time Dr Sheehan has given this possible explanation The pituitary gland is known to become hyperplastic and more vascular during pregnancy Since the gland is encased in a rigid bony compartment that cannot expand the swelling of the pituitary must cause an increased pressure within the gland This would require a higher blood pressure to maintain blood flow into the pituitary Under these conditions any drop in systemic blood pressure might greatly impair the blood flow into the pituitary and cause ischemic necrosis

Dr Nicholson we have done 24 hour radioactive iodine uptakes but not on these particular patients In our hands the 5 hour uptake has been just as reliable and is somewhat simpler particularly when treating outpatients It may be that with a different technique you could see an earlier rise in uptake after TSH but I am not so sure about that It seems reasonable that after years of atrophy some thyroid glands simply will not be able to respond to TSH stimulation within such a brief period of time This is quite similar to the delayed responses to ACTH of some of the long atrophied adrenals

Dr Thomas our doses of thyroid were for the most part 60 to 120 mg sometimes 180 mg daily I did not mean to imply that the BMR did not rise It did rise but it would rise perhaps from −40% to −20% or 25% The results were unpredictable and did not correlate well with the clinical state of the patient

analyses was prepared for histologic study Two pathologists routinely examined the sections and described their findings Later on they were reviewed by two other pathologists who kindly recorded their impressions

At convenient times the frozen specimens were divided into segments for weighing drying and ashing Aliquots were selected for nitrogen for chloride and for phosphorus sodium, potassium calcium and magnesium analyses Drying was done in an electric oven at 95 C for forty-eight hours and the difference between the weights of the fresh and dried tissue is considered to represent water content of the tissue Dried material, in minimal amounts of 0 6 N hydrochloric acid was ashed in platinum dishes at 600° C according to method of Howard [6] Fat content was determined after three ether washings of the dried material on three specimens of mucosa and two of muscularis Estimations for blood content were not made

Nitrogen was determined on frozen tissue by a modified Kjeldahl method [7] Chloride was determined on an aliquot of fresh tissue by method of Van Slyke and Sendroy [8] Ashed material tested until free from organic matter was diluted to 50 or 100 cc according to sample and stored frozen in sealed containers for estimation of phosphorus sodium potassium calcium and magnesium Phosphorus was determined by the Umbreit[9] modification of the method of Fiske and Subbarow [10] Sodium and potassium were quantified by means of an American Cyanamide Company s experimental internal flame photometer equipped with a corning fritted pyrex filter [11] Calcium was determined by the Clark Collip[12] modification of the Kramer Tisdall method and according to technic described in Metabolic Methods [13] The supernatant fluid remaining after calcium precipitation was utilized for magnesium determination by the method of Denis[14] and that of Fiske and Subbarow [15] Cations of the last five of the stomach tissues and the five colon tissues were run in duplicate and the averages are reported

Results

The data is presented in terms of wet tissue for ease of comparison to those of other investigators and because the reader obtains an easier comprehension of the results in terms of fresh tissue Fats as estimated in three gastric mucosae averaged 0 8 per cent of fresh tissue In two smooth muscle colon specimens it averaged 2 5 per cent of fresh tissue

Mucosa of Stomach and Colon

A detailed portrayal of the data and its statistical treatment is shown in Table I As the concentrations of H_2O N P Cl Na K Ca and Mg in the antrum and in the fundus of stomach mucosae are within confidence limits of their respective means the averages of the eighteen mucosal stomach

patients in The Johns Hopkins Hospital. Each patient was in a fasting state for fourteen or more hours. Tissues were selected from the antral and fundic portions of the distal segments of stomachs partially resected for duodenal ulcer (8 patients), gastric ulcer (1 patient), sarcoidosis (1 patient) who came to operation with the misconception that a hidden ulcer was the cause of repeated hematemesis. Colon tissues were obtained proximal to malignant growths. Customary preoperative injections of morphine sulfate mg 10 and atropine sulfate mg 0.6 were given to each patient. Anesthesia for each patient consisted of a combination of sodium pentothal, tubocurarine hydrochloride and nitrous oxide with oxygen. During the period of operation each patient received by vein 5 per cent glucose approximately 750 cc. None received saline. Two patients during subtotal gastrectomy and three during colon resection received 500 cc whole blood during the later half of the operation.

Serum chloride and CO_2 *estimations were made on 5 patients prior to* operation. Chloride varied from 103–106, CO_2 from 25.8–26.7 meq/l. Sodium ion as estimated on two patients was 140 meq/l. None of the patients in this series were known or considered to be in electrolyte imbalance.

The following concentrations of water and electrolytes in plasma are used in calculations for histochemical tables: H_2O = 930 gm/l, P = 2.1, Cl = 105, Na = 140, K = 4, Ca = 5 and Mg = 1.8 derived as milliequivalents per liter of plasma. Their concentrations as referred to ultrafiltrate were computed according to the equilibrium ratios of Mannery.[2]

The resected portion of the stomach or colon was freed from adhering fat *and connective tissues and opened promptly after removal from the* patients. The stomach was opened by incision along the lesser curvature except in the case of the gastric ulcer which was opened at the greater curvature. Blood and gastric juices were absorbed during gentle contact with ashless filter paper. Specimens for analysis were selected from representative areas of antrum and fundus and the mucosa was separated from the muscularis along the facile line of cleavage. Both tissues were frozen directly afterwards. Chemically clean glassware was used.

The proximal portion of the segment of colon removed at operation was selected from analyses. It was opened along the longitudinal axis. Any fecal contents were removed by a gentle stream of tap water and the surface of the mucosa and serosa gently blotted with ashless filter paper. The mucosa was separated from muscularis and both tissues were frozen.

Strips of skeletal muscle were obtained during operation from four patients (rectus abdominalis). They were treated similarly to smooth muscle and frozen.

That proportion of each specimen which was not needed for chemical

M f A rum d F d Mucosa

C h d St d d Erro M †C f I m t N	4 6 95 5±2 4 67) 18	0 43 27 7 23 ±2(0 43) 18	4 11 31 6 31 6±2(4 11) 18	1 95 62 6 ±2 1 93) 18	10 8 80 5±2(2) 18	2 1 80 80 7±2(2 21) 18	1 59 8 1 8 1±2(1 69) 18	0 65 4 4±2 0 65) 6							
C f Mucosa															
(1) D C ♀ C us S g d	5 8	8	63 9	51 1	5 2	4 5	8 1	2 6	430	330	3 8	154	121	11	2 8
2 M R ♂ C T C l	810	25 0	34 5	93 0	190 0	9 0	24 4	12 3	970	1270	0	?	?		?
3 L C ♀ C D Col	90	30 1	92 1	9 4	109 5	63 0	70 4	10 3	819	8	0	7		?	?
(4) F B ♀ C S g m l	804	8	54 6	4 9	109 0	60 0	11 3	16 1	630	770	134	119	7 6	5	109
(5) I M ♂ C T Col n	909	4	45 1	45 5	5 0	50 0	14 0	0	394	320	411	107	116	9	51
St d d Err Mea †C f L t	4 506 06±2/7 42)	1 38 1 9 21 9±2(1 38)	8 04 6 1 6 1±2 8 04)	10 1 0 3 0 3±2 10 21)	19 15 109 109 ±2(19 15)	5 66 60 3 60 3± (5 66)	7 5 13 2 15 2±2(3 5)	2 19 12 6 12 6±2(3 19)							

F t cell la H_2O tal lat f fro th ss mj t that hlr i th pj ; ut mo t f aod are t rl d t travell l ; l ase f t se 1 t acell 1 t
d ff re re bet ee s f s sa t d leme l l) rcd aod t acell l 1
Figure n d g t d d col na der ed f m se m d t n t H_2O—930 C1 105 P 2 N —140 K 5 C —5 d Mg 1 8 se; Lew m d fr 11 15 n
to p ete t d M ; I lae d bt la fro ao re
† C fi le L t

TABLE I

Histochemical Data Derived from Mucosa Tissue Analyses

Patient—Diag	H_2O	N	P	Cl	Na	K	C	Mg	$(H_2O)_E^{Cl}$	$(H_2O)_E^{N}$	$(H_2O)_I$	[P]	[K]	[C]	[Mg]
St mach 4 t m M sa															
	gm/kg t		m q/kg t						gm/kg t ue			m q/kg t t lu. H_2O			
(1) A G ♀ ½ ro hoats	809	3 4	4 4	69 2	9 0	66 8			600	560	249	95 5	36		
(2) R C ♀ D Ulcer	810	5 0	16 5	54	6 6	67 0			466	53	344	43 5	188		
(3) P B ♂ C Ulcer	810	22 9	43 6	63	92 8	59 5			550	659	60	154	12		
(4) L V D ♀ D Ulcer	814	23 2	13 2	40	69 2	1 5			470	450	394	36	1 8		
(5) S LeB ♂ D Ulcer	803	2 5	1 9	56 2	8 8	62 0			487	584	316	57	189		
(6) C R S ♂ Pyl c Ul	810	19 1	49 5	8 3	9 0	52 8	12 4		690	683	130	3 0	388	9	
(7) H H ♂ D Ulcer	53	6 4	50 0	63 2	2	6 2	6 2	10 3	548	511	242	200	30	1 6	40
(8) A C ♂ D Ulcer	800	2 1	46	66 6	84 8	53 8	18	7 3	5 6	600	224	200	0	C ?	8
(9) W B ♂ D Ulcer	806	22 9	29	59 8	97 5	58 3	6 0	5	509	69	97	99	199	14	1
St n l d I	6 23	0 6	5 08	3 2	3 56	2 66	2 49	1 35							
M	802	3	32 2	6	83	63	10 2	8							
†C f L t	80 ±2(6 3)	3±2(0 6)	3 2±2(5 09)	62±2(3)	83±2(3 56)	63±2(2 66)	10 2±2(49)	8±2(1 35)							
St mach F d s Mu															
(1) T F ♂ D Ulcer	800	21 9	12 8	61 3	6 0	55 3			510	480	390	36 6	162		
(2) R C ♀ D Ulcer	800	27 0	21 0	1 5	66 2	57 5			670	468	334	60	169		
(3) P B ♂ C Ulcer	80	4 3	56 0	62 3	5 0	6 2			550	528	52	1	256		
(4) L V D ♀ D Ulcer	803	3 6	10 0	52	1 0	63 3			456	460	347	26	1 6		
(5) S LeB ♂ D Ulcer	95	20 0	8 0	54 6	63 5	60 3			4 3	449	338	2	190		
(6) C R S ♂ P I Ulc	704	4 1	28 0	73 4	91 4	57			635	642	159	157	349		
(7) H H ♂ D Ulcer	40	3 8	45 2	61 0	85 0	38 4	6 7	6 2	579	600	211	209	1 2	23 2	6 9
(8) A C ♂ D Ulcer	900	21 0	3 7	67 5	83 0	2 0	4 9	7 1	598	598	232	173	5	13 2	8 3
(9) W B ♂ D Ulcer	91	24 3	54 4	65 9	99 3	47 2	4 3	7 5	509	07	2 2	245	70	10	9 6
St d 11 ro	6 84	0 49	5 7	2 38	4 14	3 8	0 72	0 38							
M	89	21	34 1	63 3	7	5	5 3								
†C f 1	±2 4) 2	7±2	±2 5 7) 63	±2	77 ±	±									

specimens except one which is from the same stomach If this represents water loss during manipulation of tissue concentrations of electrolytes should be higher than recorded

Nitrogen concentration of mucosa (Table I) is less than in skeletal muscle It is slightly more concentrated in colon than in stomach mucosa It does not vary in concentration with phosphorus or potassium

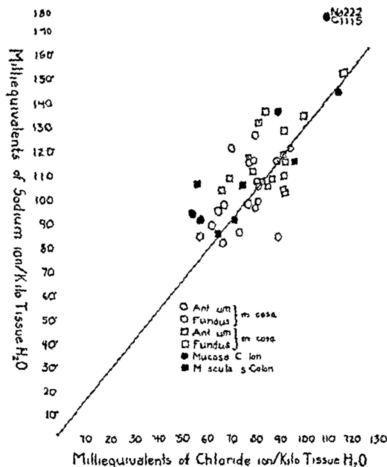


FIG 1 Relation of sodium chloride ratio in tis ues analyz d to sodium chloride ratio 1 233 in ultrafiltrate indicated by d agonal line Ultrafiltr ite calculated from serum electrolytes and water (2)

tissues may be a satisfactory representative of each group Calcium in statistically significant amount is more concentrated in the antral than in the fundic mucosal tissues of the stomach however, the small number of tissues analysed for the ion and for magnesium may be better represented by the means of the combined mucosal group Thus the mean of the concentrations of stomach mucosa are H_2O = 795, N = 23 9 gm/L wet tissue P = 31 7, Cl = 62 6 Na = 80 5 K = 60 2 Ca = 7 7 and Mg = 7 3 meq/L wet tissue Comparison of these data to those of the five colon mucosae reveals certain differences In this tissue the mean of the concentrations are H_2O 806 N 24 9 gm/L wet tissue P 62 1 Cl 70 3 Na 109 7, K 60 3 Ca 15 2 and Mg 12 6 meq/L wet tissue In the colon the range of chloride is 40 to 93 meq/Kg in the stomach 49 to 73 4 meq/Kg Sodium in the colon ranges from 75 to 180 meq/Kg and in the stomach 66 2 to 99 3 meq/Kg

The concentration of potassium in mucosal specimens is considerably in excess of the amounts reported in connective tissue[15, 16] Phosphorus is also more concentrated in the current analyses than in connective tissue[17, 18] That the ratio of the means for phosphorus and for potassium in stomach mucosa is 0 52 and for the mucosa of the colon is 1 03 may be of significance in gastric secretion An intracellular transport of chloride or bicarbonate could be a means of balancing the negatively and positively charged ions

Calcium and magnesium concentrations in mucosal tissues are greater than in ultrafiltrate both ions are notably more concentrated in the colon than in gastric specimens Whereas there is more calcium in the antral than the fundic mucosa of the stomach the amounts of magnesium in antral and fundic stomach mucosal specimens are not appreciably different

Calcium and magnesium have been reported[15] in rabbit tendons in concentration approximating the present analyses of mucosa In human and dog skin[19, 0] which are partially connective tissues concentrations of Ca 2 1 and 3 03 mm/L and Mg 2 7 and 3 mm L have been reported Concentrations of these ions in glandular tissue have been reported as follows pancreas[1]—calcium 8 and magnesium 14 Salivary—calcium 9[m] Testes—calcium 5 and magnesium 8[2] in another Testes[3] series—calcium 1 7 and magnesium 10 as meq Kg tissue An analyses of liver is reported[4] for calcium 2 and magnesium 31 0 meq I intracellular water

The water content of mucosal tissue varies from specimen to specimen but approaches 800 gm/L tissue The highest and lowest results are 826 and 740 gm L The latter is substantially lower than water content of other

pecimens except one which is from the same stomach If this represents water loss during manipulation of tissue, concentrations of electrolytes should be higher than recorded

Nitrogen concentration of mucosa (Table I) is less than in skeletal muscle It is slightly more concentrated in colon than in stomach mucosa It does not vary in concentration with phosphorus or potassium

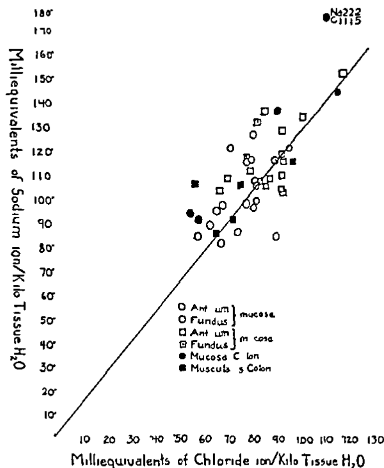


FIG 1 P lation of sodium-chloride ratio in ti ues analyzed to sodium-chloride ratio 1 233 in ultrafiltrate indicated by diagonal line Ultrafiltrate calculated from serum electrolytes and water (9)

TABLE II

Histochemical Data Derived from Smooth Muscle Tissue

P t t—D gn	H_2O	N	P	Cl	Na	K	C	Mg	$(H_2O)_E$	$(H_2O)_I$	(H O)	[P]	[K]	[Ca]	[Mg]
St mach 4 l m M sc l s															
	g /kg t		*g/kg t*						*g /kg tis e*			*meq/kg I H O*			
(1) A G ♀ S rco dos	820	24 3	51 0	4	8 9	51 2			645	590	200	250	44		
(2) R C ♂ D Ulce	818	6 8	49 8	74 0	84 0	50 0			639	591	227	09	50		
(3) P B G Ulce	800	6 8	4 9	6 4	86 0	53 3			660	606	194	32	65		
(4) L V D ♀ D Ul	820	3 3	39 7	59 3	89 0	51 8			514	6 6	306	126	160		
(5) S LeB ♂ D Ulce	9	2 2	42 5	54 2	81 5	62 8			468	5 4	324	127	187		
(6) C R S ♂ Pyl Ulce	90	6 8	60 4	66 9	82 8	60 0	9 6		5 8	598	222	69	63	37 0	
( ) H H ♂ D Ulce	806	22 0	43 2	6 5	102 7	36 0	8 2	1 5	663	23	137	300	249	43 0	2 9
(8) A C ♂ D Ulce	810	21 6	50 0	8 3	92	64 1	8 4	7 2	690	5 8	23	209	64	24 9	26 2
(9) W B ♂ D Ulce	9	30 4	6 8	0 0	109 0	38 4	5 6	4 2	605	69	192	135	189	18 9	16 7
St I I E ro	4	0 95	3 09	2 80	3 30	3 35	0 84	1 65							
M	805	5 5	45 6	0	89 4	53	8 0	4 3							
†C f L m t	805±2(4)	25 2±(0 95)	45 6±2(3 09)	0±2(2 80)	89 4±2(3 3)	53±2(3 35)	8±2(0 84)	4 3±2(1 65)							
St mach F d M ul s															
(1) —	—	—	—	—	—	—	—		—	—	—	—	—	—	—
(2) R C ♂ D Ulce	92	19 2	56 6	82 0	105 3	36 1			723	6	69	512?	49 ?		
(3) P B ♂ G Ulce	515	28 6	50 0	8 5	93 0	47 2			693	653	162	300	90		
(4) L V D ♀ D Ulcer	6 6	27 6	48 0	6 4	96	49 2			594	637	24	199	190		
(5) S LeB ♂ D Ulce	812	2	38 0	66 7	90 0	45 5			5 8	639	234	100	195		
(6) C R S ♂ Pyl Ulce	800	6	56 8	3 3	90 5	62 5	4 3	2 6	635	640	165	337	363	11 5	9 1
( ) H H ♂ D Ulce	98	21 9	42 6	68 0	105 0	44 0	5 2	5 1	500	40	208	198	199	14 4	19 8
(8) A C ♂ D Ul	96	23 2	57 0	6 4	87 0	51 7	5 0	6 1	663	614	182	300	271	13 8	28 8
(9) W B ♂ D Ulcer	81	24 4	45 4	92 2	118 5	45 2	4 3	16 1	796	812	0	?	?	?	?
St d d E r	5 07	1 13	2 53	3 09	3 6	2 65	0 3	2 06							
Me	803	25 0	49 3	75 5	98 2	47 6	4 7	7 5							
†Co f I m t	803±2(5 07)	25±2(1 13)	49 3±2(2 53)	5 5±2(3 09)	98 2±2(3 76)	47 6±2(2 65)	7±2(0 23)	7 5±2(2 96)							

M f A m nd f nd us M c l

St d d E ro	3 10	0 5	2 01	2 12	2 63	2 1	0 3	1 82							
M	804	25 2	47 3	2 6	93 6	50 4	6 3	6 1							
†Co f L t	804±2(3 1)	5 2±2(0 71)	4 3±(01)	2 6±2(2 12	93 6±2(2 63)	50 4±(2 21)	6 3±(0 3)	6 3±2(1 82)							
N	1	17	1	t	17	17	8	7							
C l M c l															
(1	57	2 1	54 2	50 8	65 4	42	3 8	1 8	410	400	317	169	1 7	6 6	2
(2	840	2 0	33 2	63 0	3 6	67 5	4 3	5 2	515	518	372	100	700	6 8	13 0
(3)	810	6	61 2	80	106	65 0	8 8	6	7 0	50	100	?	?	60	657
(4)	90	21 8	70 1	50 5	82 0	6 5	3 3	9 2	524	590	56	1	210	5 1	12 6
(5)	808	5 3	45 1	45	86 0	50 0	11 0	15 0	39	606	411	107	118	72 0	33
St d d Frr	14 15	35	35	6 03	4 7	4 85	1 54	2 23							
M	99	24 2	42 8	60 1	82 0	57 4	6 2	7 5							
†Co f L t	99±(14 15)	24 2±2(7 35)	42 8±2(35)	60 1±2(6 03)	8 ±2(4 7)	57 4±2(4 85)	6 ±2(1 54)	5±2(2 3)							

E t cell la H_2O c l i t d fro the as m t o th t l b f th p ro t m t f d m re rest t I t t acell la p l ase f tue I t acell la w t s d ff rence bet ee grams f tue t l lesser f hl d d m t cell l r w t

F g re 4 ugl t-a ded col m d rn ed from seru i t t H_2O—930 Cl—105 P 2 N —140 1—5 C —5 d Mg—1 8 eq L seru m l fro n the Do n n tt p se t d M n ry [1] F n l nd yn t l from so ces [2]

†C fi l ce L t

Sodium Chloride Ratio

Sodium and chloride ratios in the mucosa of the stomach and colon are depicted in Figure 1 It is evident that the majority take positions near a line from the point of origin to the point representing sodium chloride ratio of ultrafiltrate The points above the line represent an excess of sodium and below an excess of chloride *with respect to the proportions of the ions in* ultrafiltrate

A small excess' chloride is present in 2 antral and 2 fundic specimens in colon tissue sodium excess is noted in four Antral and fundic tissue ratios to the same degree approach the ' line of ultrafiltrate In consideration of the limitation of hydrochloric acid production to cells of the fundus of the stomach this finding has elements of surprise It is also worthy of note that *the mean potassium concentration in both stomach tissues is approximately* equal

Intracellular ions

The concentrations of sodium and chloride in the proportions of plasma ultrafiltrate, are calculated as grams of extracellular water required for each ion (Table I) Calculations are based on the assumption that chloride, with appropriate amounts of sodium phosphorus, potassium, calcium and magnesium is extracellular In estimating grams of intracellular water the lesser of the chloride or sodium values are deduced from grams of tissue water The intracellular *concentrations of phosphorus potassium* calcium and magnesium are calculated after reducing from their tissue concentrations the amount contained in the extracellular phase of tissue water

Intracellular concentrations that constitute a physiologic state are difficult to assess In ten mucosal stomach specimens and two of the colon the calculated values of cellular potassium do not differ substantially from the proposed normal values in varied tissue [2] The function of potassium calcium and magnesium in glandular tissue is at best hypothetical and as the proportion of the individual ions in a free or bound state is unknown the measure of physiologic cation concentrations cannot now be assayed

Intracellular concentrations of phosphorus of the stomach mucosa and in the mucosa of two colons implies an anion *deficiency unless another* negatively charged ion enters the cell

In stomach mucosa the intracellular concentration as calculated of calcium ranges from 10 2 to 23 2 and of magnesium from 17 to 40 meq/L intracellular water In colon mucosa the concentration of calcium and magnesium cannot be calculated in three tissues as there is small or no intracellular space In the other two specimens calcium is 11 7 and 29 and magnesium *2 8 and 51 meq/L intracellular* water

Histology of tissues

An evaluation of the chemical data is of greater significance when the relationship of intracellular water and electrolyte concentrations to the histopathology of individual tissue is available. Nine stomach and five colon mucosal specimens are considered to have normal histologic character

TABLF III

Histochemical an l Histopath logic 1 ialyses of Mu osa of St mach and Col n

N	T	$(H_2O)^{Cl}$	$(H_2O)^N$	(H_2O)	[P]	[K]	[C l]	[Mg]	H t path l g c Descriptio	D gn
		gm/kg t s			meq/kg t cel l H_2O					
1	A	800	500	248	95 5	2 ?			Oed ma erosio s Sel man bod ro nd cell filtrat n	ro sis
10	F	540	480	320	30 5	16			N al tissu	D xle l ul
2	A	466	538	344	43 5	1 9			Normal t s	Duod nal ulce
	F	620	466	334	60 0	169			N rm l tis	
3	A	550	653	60	154	21			Small erosions oed ma r d cell filtr t n	Gast lce
	F	550	6 9	25	217	.56			S ll ros oe l ma ro l cell infil rat n	
4	A	470	480	394	35	378			N a l tissues	D od n l ulc
	F	456	460	4	6	1 6			Norm l tis es	
5	A	467	564	316	5	180			N al t ssu	D d l lce
	F	4 3	449	356		190			N al tis es	
6	A	690	683	1.6	3 0	345	97?		Fre l h m rrhag oed ma	D od l lce
	F	6.5	64.	159	15	319			Oed m ro l ce l g t tis scarr g	
	A	548	511	4	700	30	1 6	40	Chronic g tr t	C r l l
	F	5 9	600	211	709	1 2	23 2	26 9	N m l t su	
8	A	5 6	600	4	200	220	6	28	Ep tty ro ll t g t tis	D od l lcer
	F	589	599	21	1 3	3??	13 2	25 3	N l tiss	
9	A	509	68	29	99	198	4	17	O ras n l fo l round cel in	D od l lce
	F	569	71?		45	20	10 2	29 8	b th t sue	
						Colon				
1		450	530	2 0	168	121	11	2 8	N l tiss	C col
2		620	1 1	0	?	?	?	?	N mal tissu	C colon
3		819	85	0	?				Norm l tiss	C colo
4		650	70	151	3497	3 6	59?	300	N mal t es	C col
5		304	5 ?	414	307	116	2?	50	N mal tissue	C colon

Gram f w t re; v l b el lorid d sodi propo t f lt fls t ntracell l w te dif feren bet een tissue wat r l lease f l l d w l m e l n C llul ion as T ble I I terp t tio l l at logy sect ons rel te to A trum n l F l nd re iens f st ch d col m cor N abers l 10 f to pat t in the d f l t ng in T bl l

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phorus potassium calcium and magnesium would be contained within connective tissue and in ionic equilibrium with lymph and plasma The requirements of this hypothesis are fulfilled by the ionic intracellular patterns of ten stomach and two colon mucosae in which the concentration of potassium is within limits that are considered normal In two of these tissues occasional foci of round cells are noted on microscopy

Eight mucosal tissues require extracellular space of such dimensions that intracellular potassium if not bound to cellular constituents appears unreasonably concentrated In these tissues all but one of which presented abnormal histology some chloride or sodium or both are presumed to be intracellular This suggests a pre secretory or secretory metabolic state

The undetermined amount of chloride in gastric tubules and chloride and sodium in the faveolae and adhering to the mucous membrane may be deducted from the concentrations of the ions thus diminishing the calculated extracellular and increasing the intracellular phases of stomach mucosal tissues

It appears reasonable that chloride or sodium may be bound by extracellular organic compounds or enter the cells of the gastric tubules However recent studies[5] show that at the Ph of serum these ions are not bound by proteins of connective tissue Furthermore Bensley[6] Lason[77] and Gersh[78] have not been able by histochemical technics to demonstrate chloride in parietal cells By their different technics each has revealed abundant amounts of chloride in adjacent connective tissue and some in zymogen cells and the lumen of gastric tubules

That chloride and also sodium enter the lumen of the stomach by transport across the parietal and other cells or via spaces between them is obvious The data presented suggest that the increased gastric secretion associated with peptic ulcerations may be in part explained by the evidence that chloride under the stimulus of pathology or the adaptation to stress or both enters cells of the gastric tubules especially the parietal

Colon mucosa does not as readily adapt itself to the conception that glandular cells represent the intracellular phase and connective tissue the extracellular phase In three of five tissues the concentrations of chloride and sodium in proportions of extracellular filtrate leave no intracellular space Therefore in these tissues it appears that undetermined amounts of sodium chloride and other ions may be in transit through epithelial cells It is difficult to conceive that an absorbing membrane acts otherwise especially so when ions leave the gut against a concentration gradient[79]

In two colon tissues the limits of extracellular space are consonant with reasonable concentrations of intracellular ions It is suggestive that the latter may be resting and former actively absorbing tissues

istics (Table III) Nine specimens reveal evidence of histopathology the single tissue—antrum with abundant evidence of sarcoidosis the antral and fundic specimens from the patient with a gastric ulcer, both specimens from patient (LeB) with an ulcer at the pylorus (classified as duodenal) and the antral and fundic specimens from a patient (W B) with a duodenal ulcer and the antral specimens from two patients with duodenal ulcers

The greater proportion (seven) of stomach mucosal tissues with normal histologic structure are identified with tissues in which the intracellular phase contains three hundred or more grams of tissue fluid In these compartments potassium values range from 162 to 190 meq/L In one fundus specimen histologically normal potassium concentration in a small intracellular phase (211 gram) is 172 meq/L To this group of tissues may be added two tissues from the same stomach (W B) with evidence of slight to moderate infiltration of round cells in focal areas and in which potassium concentrations are 188 and 202 meq/L intracellular water

These data are consistent with the hypothesis that chloride with appropriate amounts of sodium is restricted to the extracellular phase of tissue

In the remaining normal specimen which also has a small intracellular phase potassium concentration is calculated as 322 meq/L intracellular water

In seven stomach mucosal specimens with micropathologic changes, the size of the intracellular space is less than three hundred cc and potassium concentrations are elevated 212 to 380 meq/I In these tissues the evidence of tubular cell abnormality is limited to small areas or lacking No evidence is presented which may be interpreted as interfering with their secretory functions—a characteristic which is well attested clinically

The specimens of colon mucosa are considered as histologically normal but high chloride and sodium concentrations in three either negate intracellular space as in two or so restrict it that its potassium concentration is excessive In the two remaining specimens the concentration of intracellular potassium is 116 and 121 meq L which is consistent with the assumption that chloride is an extracellular ion

Histochemical Considerations

Stomach mucosa may be considered as divided anatomically into two major partitions—*glandular cells and connective tissue* From consideration of data here presented it is suggested that chemically its glandular phase may be referred to as intracellular and its connective tissues as extracellular Thus chloride with appropriate amounts of sodium phos

in the colon musculature are remarkably alike There is however, a statistically significant greater amount of calcium in the antrum than in the fundus The values for calcium[2] are somewhat greater than those reported in smooth muscle of frog and uterus of the rat and magnesium is less concentrated in human gastro intestinal muscle than rat uterus Small amounts of magnesium are reported in one antral fundic and colon tissue for causes which are not apparent but appear to represent actual conditions within the muscle tissue This is surprising for it is thought that muscle cells tend to retain this ion

Sodium-chloride Ratio

Further clarification may be obtained from the dispersal of points indicating the sodium chloride ratio of smooth muscle tissue in relation to the sodium chloride ratio of ultrafiltrate (Fig 1) Some points fall directly on the line connecting the sodium chloride ratio of ultrafiltrate (1 23) to point of origin those above indicating sodium excess and those below chloride excess In a few tissues there are substantial variations between the sodium chloride ratio of muscularis and that of ultrafiltrate However in the majority of tissues the major proportion of these ions are contained within smooth muscle tissue in the proportions of ultrafiltrate

Intracellular Ions

If the assumption that chloride is restricted to extracellular space is applied to this tissue as to skeletal muscle the dimensions of extracellular phase will vary with the concentration of chloride or sodium in each tissue Therefore the concentration of potassium in intracellular fluid varies with the size of the extracellular compartment

Intracellular potassium concentrations in the musculature of six of seventeen stomachs range from 160 to 198 and in three colon specimens from 116 to 200 meq L intracellular water They are similar to concentrations in the tissues reported as normal[2] In the remaining eleven stomach and two colon muscle tissues the compartment containing sodium and chloride in the proportions of ultrafiltrate attain dimensions that require a large portion of tissue fluid and little or no space remains for intracellular ions Concentrations of cellular phosphorus tend to parallel those of cellular potassium (Table II)

Intracellular concentrations of calcium in smooth muscle are considerably greater than in the cat[33] and the dog[4] which are reported as 2 meq/L in each animal In antral tissue the ion varies from 18 to 13 and in the fundus from 11 to 14 4 meq L intracellular water In only two of these specimens is the cellular concentration of potassium consonant with the assumption that chloride is extracellular and in these tissues intracellular calcium is calculated as 18 and 14 4 meq L In colon smooth muscle the calculated cellular concentrations of calcium are 6 6 6 8 L and 22 meq/L intracellu

Muscularis of Stomach and Colon

The same elements are quantified in these tissues as in the mucosa (Table II) The similarity of respective ions excepting calcium and magnesium, in the antrum and fundus of stomach muscle tissues is evident The means of their concentrations in seventeen smooth muscle stomach tissue are H_2O 804 N 25 2 gm/L P 47 2 Cl 73 3 Na 94 2 K 49 0, Ca 6 2 and Mg 6 0 meq/K tissue, and in colon musculature H_2O 799 and N 24 2 gm/Kg P 42, Cl 60 1 Na 80 Ca 6 2 and Mg 7 5 meq/Kg tissue

Analyses of strips of abdominal muscle obtained from four of the patients average H_2O 740 and N 32 2 gm/I Cl 15 Na 35 and K 89 meq/K tissue

The impressive result of the chemical analyses of smooth muscle tissue of stomach and to a slightly less degree of colon is the high concentration of sodium and chloride—a striking contrast to the lesser concentrations of these ions in skeletal muscle It is also impressive that potassium concentration is considerably smaller in gastro intestinal muscularis than in skeletal muscle

Stomach and colon smooth muscle contains more connective tissue than skeletal and also differ in the absence of sarcolemal membrane surrounding the muscle fibers These anatomical differences may explain some of the electrolyte differences in the structures

Water and Nitrogen

The water content of smooth muscle tissues is greater than in skeletal tissue analysed and in numerous reports[2] It is not strikingly different from that of component mucosal complements and it is similar to those reported for smooth muscle tissues[3 30 31 3 33]

Nitrogen is less concentrated in smooth muscles than in the skeletal muscles analysed and in numerous reports in the literature No direct association of its concentration to those of phosphorus or of potassium is apparent

Phosphorus and Potassium

Potassium concentration in frog[3] smooth muscle is reported to be 83 *whereas in the stomach muscle of steer*[31] *and rabbit*[3] *and in the uterus of the* rat[33] it is respectively 94 99 9 and 93 meq/Kg wet tissue In the present study the mean concentration of potassium in stomach muscle is 50 4 ± 2(2 21) and in colon 57 4 ± 2(4 8))

In stomach muscle tissue the concentrations of phosphorus and potassium tend to approximate each other in contrast to the higher level of potassium with respect to phosphorus in colon musculature

Calcium and Magnesium

The means of calcium 6 3 ± 2(2 73) and magnesium 6 3 ± 2(1 82) in stomach and 6 2 ± 2(1 >4) for calcium and 7) ± 2(2 23) for magnesium

in the colon musculature are remarkably alike There is however a statistically significant greater amount of calcium in the antrum than in the fundus The values for calcium[29] are somewhat greater than those reported in smooth muscle of frog and uterus of the rat and magnesium is less concentrated in human gastro intestinal muscle than rat uterus Small amounts of magnesium are reported in one antral fundic and colon tissue for causes which are not apparent but appear to represent actual conditions within the muscle tissue This is surprising for it is thought that muscle cells tend to retain this ion

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The same elements are quantified in these tissues as in the mucosa (Table II) The similarity of respective ions excepting calcium and magnesium in the antrum and fundus of stomach muscle tissues is evident The means of their concentrations in seventeen smooth muscle stomach tissue are H_2O 804, N 25 2 gm/L P 47 2 Cl 73 3 Na 94 2 K 49 0, Ca 6 2 and Mg 6 0 meq/K tissue and in colon musculature H_2O 799 and N 24 2 gm/Kg P 42 Cl 60 1, Na 80 Ca 6 2, and Mg 7 5 meq/Kg tissue

Analyses of strips of abdominal muscle obtained from four of the patients average H_2O 740 and N 32 2 gm/L Cl 15 Na 35 and K 89 meq/K tissue

The impressive result of the chemical analyses of smooth muscle tissue of stomach and to a slightly less degree of colon is the high concentration of sodium and chloride—a striking contrast to the lesser concentrations of these ions in skeletal muscle It is also impressive that potassium concentration is considerably smaller in gastro intestinal muscularis than in skeletal muscle

Stomach and colon smooth muscle contains more connective tissue than skeletal and also differ in the absence of sarcolemal membrane surrounding the muscle fibers These anatomical differences may explain some of the electrolyte differences in the structures

Water and Nitrogen

The water content of smooth muscle tissues is greater than in skeletal tissue analysed and in numerous reports It is not strikingly different from that of component mucosal complements and it is similar to those reported for smooth muscle tissues[3 20 21 2 33]

Nitrogen is less concentrated in smooth muscles than in the skeletal muscles analysed and in numerous reports in the literature No direct association of its concentration to those of phosphorus or of potassium is apparent

Phosphorus and Potassium

Potassium concentration in frog[3] smooth muscle is reported to be 83 whereas in the stomach muscle of steer[21] and rabbit[3] and in the uterus of the rat[33] it is respectively 94 99 9 and 93 meq/Kg wet tissue In the present study the mean concentration of potassium in stomach muscle is 50 4 ± 2(2 21) and in colon 57 4 ± 2(4 85)

In stomach muscle tissue the concentrations of phosphorus and potassium tend to approximate each other in contrast to the higher level of potassium with respect to phosphorus in colon musculature

Calcium and Magnesium

The means of calcium 6 3 ± 2(2 73) and magnesium 6 3 ± 2(1 82) in tomach and 6 2 ± 2(1 54) for calcium and 7 5 ± 2(2 23) for magnesium

TABLE IV

Histochemical and Histopathologic Analyses of Muscularis of Stomach and Colon

No.	T	$(H_2O)^{Cl}$	$(H_2O)^{Na}$	(H_2O)	[Cl]	$[K]_i$	[Cl]	$[Na]_i$	Histopathologic Description	Diagnosis
		gm/kg t	ue		meq/kg	t acell	H_2O			
1	A	645	620	700	2.0	244			Schaumann bodies S ll foci f ro d cells	Sarcoidosis
10	F	—	—	—	—	—				
2	A	839	891	2??	209	250			Normal m sculat re	Duodenal lcer
	F	23	726	69	512	492			N r al m sculature	
3	A	660	606	194	232	?65			Scarr g d rou d cell filtratio	Gastric lcer
	F	693	653	1?	300	290			Scarring d ro d cell infiltrat n	
4	A	514	576	306	126	160			N l sc la is	Duodenal lcer
	F	584	63	24	194	190			Norm l m scula is	
5	A	468	5 4	324	12?	1??			N mal muscularis	Duodenal ulcer
	F	5 9	639	234	160	185			N rmal sculars	
6	A	5 8	5?5	2??	268	263	3		Th k m sc lat re scarring d ro d cell infiltratio	Duodenal lcer
	F	635	640	155	33	363	11 5	9 1	Thick musculat scarri d ro d cell filtrat	
7	A	663	23	13	300	249	43	2 9	Scarr g near p l ru	Duodenal lcer
	F	590	740	209	198	198	14 4	19 6	Normal tissue	
8	A	690	5 8	232	?09	264	? 9	26 2	T al ro nd cell filtratio	Duodenal lcer
	F	663	614	182	300	2?1	13 8	26 6	Slight d ma	
9	A	605	69	19?	135	198	15 0	16	Sl ht ed a	Duodenal lcer
	F	96	812	0		?			Ed ma f muscles d scarring	
						Colon				
1		440	4.0	317	169	127	6 6	2 7	N mal tiss	Carcinoma
2		545	518	322	100	200	6 8	13 0	N mal tiss	Carcinoma
3		710	50	100	?		60 0	65 0	N mal tiss	Carcinoma
4		524	580	2.6	4	240	5 1	32 6	N m l tiss	Carcinoma
5		397	606	411	116	116	?2 0	35 0	N mal tissue	Carcinoma

Grams of w ter req ired f 1 k nd d sod m in proportions f ltrafiltrate intracell lar wat d f fer nce betwee tissue w ter d leme f blo l sod m col mns Cell lar ions as T ble I f terpre t tio f histology sectio late to A t m d F f dus pec m f to ach l col use lari N be 1 10 f to patie t the l f listing T bl II

tissue and muscle fibers of the muscularis from mesenchymal cells may be a factor in the function of this system

DISCUSSION

One of the more important results of this study is the demonstration that chloride concentrations of the antral and fundic areas of stomach mucosa are of about the same value

lar water It is not unlikely that a portion of calcium calculated as intracellular is bound by connective tissue proteins

In three muscle specimens intracellular magnesium concentration is notably small In two specimens in which chloride may be restricted to the extracellular phase the value of the ion is 16 7 and 19, and in the three in which chloride is presumed to enter muscle cell fibers concentrations are 26 2 and 26 6 meq/l intracellular water In the colon smooth muscle concentrations of intracellular magnesium range from 13 to 35 meq/l Most of these values are not unlike those reported for skeletal muscle in the cat[33] and the dog[34]

Histology of Tissues

Comparison of chemical analyses to histopathology (Table IV) of smooth muscle tissues reveals some relationships that may be consequential Smooth muscle tissue to a lesser degree than their mucosal components are subject to the influences of disease of the duodenum In six tissues in *which the size of intracellular space is commensurate with reasonable con*centrations of potassium the muscular elements are considered normal or to contain trivial evidence of round cell foci or oedema

The antral muscularis from the patient with sarcoidosis and both muscle tissue specimens associated with gastric ulcer reveal histopathologic changes The fundic tissue from Case 9 (duodenal ulcer) shows evidence of considerable oedema and scarring of the muscles In these four specimens intracellular potassium concentration is considerably elevated or there is no space available for intracellular electrolytes It is thus suggestive that pathologic changes may influence distribution of ions

The colon musculature is considered as normal in each specimen except the third in which some oedema is present High concentrations of chloride and sodium are demonstrated in this tissue

The seven remaining histologic sections of the stomach appear normal or reveal minimal evidence of pathology and are identified with tissues in which cellular potassium concentrations may be considered excessive Consequently smooth muscle tissue the histologic characteristics of which are considered normal or with trivial pathologic changes may contain sodium chloride and potassium in concentrations commensurate with isotonicity of cellular potassium On the other hand the cellular cation may be concentrated

Therefore it appears that in the muscularis of stomach and colon chloride with appropriate amounts of sodium and other ions may in some metabolic states be restricted to the extracellular connective tissue phase In other states presumably physiologic chloride may be transported across the limits of smooth muscle fibers The common origin of connective

TABLE IV

Histochemical an l Hist patholog c Analyses of Muscula is of Stomach and Colon

N	Ti	(H₂O)C	(H₂O)	(H₂O)	[Pk]	[Na]	[C l]	[Na]	Histopatholog Descr pt	Di gnos
		gm kg t		ue	meq kg	t		l/l H₂O		
1	A	645	620	708	250	244			Seba um n bc les F all f ve (ro) d cells	S rco l ma
10	F	—	—	—	—	—				
2	A	639	591	2"	209	250			N rr ial m scular re	Duo l l ler
	F	23	28	69	512?	4?			N rm l m scular re	
3	A	660	606	194	23	265			Sca ing a d ro d cell filtration	Gast ic lcer
	F	693	653	165	300	290			Scarr g d ro d cell filtrat	
4	A	614	6"6	306	196	160			N mal usc laris	Duod nal lcer
	F	394	83	12	198	190			N ml m scula is	
5	A	468	5 4	371	12"	18			N r ml uscula	Duod l lcer
	F	5 8	639	234	160	185			N m l m scularis	
6	A	5 8	586	2""	"8	283	3		Thick n usculature scarring 1 ro d cell infiltrat	Duodenal lcer
	F	635	640	1 5	33"	363	11 5	9 1	Thick m scular r scarr ng n l ro d cell filtration	
7	A	663	723	43	300	249	43	2 9	Scarring ear p lcru	Duod n l lcer
	F	590	740	208	199	198	14 4	19 6	N mal tiss	
8	A	690	5 8	232	209	264	24 0	26 2	T al d cell filtrat	Duod nal l e
	F	663	611	18	300	"1	13 8	26 6	Sl ght f m	
9	A	605	69	192	135	199	15 0	16	Sl ght d ma	Duodenal lcer
	F	46	812	0			>		Fd m f n scle nd scarr g	
									Colon	
1		440	460	31	169	12"	6 6	2	N m l tiss	C ma
2		545	515	3""	100	200	6 8	13 0	N mal tiss e	C rcin ma
3		710	50	100	?		60 0	65 0	N al tiss	C rc ma
4		5 4	590	256	4	210	5 1	32 6	N mal tissu	C rc noma
5		39	605	411	116	115	72 0	35 0	N mal tiss e	Carc noma

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tissue and muscle fibers of the muscularis from me enchymal cells may be a factor in the function of this system

DISCUSSION

One of the more important results of this study i the demonstration that chloride concentrations of the antral and fundic areas of stomach mucosa are of about the same value

Previous investigators[7] determined the chloride and sodium concentrations of the fundus and antrum of the stomach mucosa of rats and rabbits and demonstrated a greater chloride concentration in the fundus. It was also shown that in chemical equivalents chloride was greater than sodium and in some animals approached or exceeded its value in plasma. These observations have not been reproduced in man and in dogs[5] values comparing favorably with the present data have been reported. The divergence of data suggests there may be differences in the ionic patterns of stomach mucosa in some species.

Another noteworthy result is the greater average concentration of chloride, sodium, calcium and magnesium in three specimens of mucosa of the colon than in the stomach. Differences which may be related to the major activities of colon and stomach, i.e., absorption and secretion.

The concept that refers to connective tissue as the extracellular phase of stomach mucosa postulates free-diffusion equilibrium with lymph and plasma and infers a source of supply for cells composing the gastric tubules. It any also receive waste products from these cells. Glandular cells of the colon differ from those of the small intestine in that their environmental fluid is subject to less variety in composition. However, during periods of absorption fluids with varying electrolyte concentrations pass through or between the cells to enter connective tissue from which they are absorbed into blood and lymph. If the concept that chloride of colon mucosal tissue is restricted to connective tissue is sustained, absorption of electrolytes into epithelial cells requires energy output by the cell.

The results of this study are to a degree in accord with the histochemical investigations of Bensley, Lison and Gersh on stomach mucosa in which they observed independently that chloride was restricted to connective tissues and zymogen cells of the gastric tubules. Gersh's material includes specimens obtained during periods of fasting and following stimulus to hydrochloric acid secretion.

However, as chloride and sodium may enter skeletal muscle fibers so may they enter and be extruded from cells of gastric tubules. Whether the *time of transport be relatively long or short*, it is obvious that gland cells of gastric tubules receive chloride either from the surrounding connective tissues or capillaries at their basement membrane, a structure composed of connective tissue elements.

Histochemical data with respect to smooth muscle tissue may be interpreted as indicating that in some tissues chloride may be extracellular and in others may be transported into fiber cells of the muscle. The normal histologic appearance of sections made from such tissues suggest that this transport may be physiologic. If so, it answers the query of Mannery, who expressed surprise "*that the wall of the aorta is so high in chloride since the* tunica media contains smooth muscle fibers as well as connective tissue.

which if free of chloride like skeletal muscle fibers should act as a diluent reducing chloride concentration

The function of calcium and magnesium in the glandular cells is not known It is probable that calcium be bound within the cell or fixed on its membrane not to be precipitated with phosphate Magnesium if non ionized increases intracellular cation concentration to levels above those usually reported

Concentration of potassium in several gastric mucosal tissues to levels about twice that of phosphorus are noteworthy and unlike the ratios of these ions which approach unity in colon mucosa and stomach muscle Whereas phosphate is demonstrable in gastric juices[35] at values which approach its concentration in serum potassium is considerably more concentrated in gastric juices than in serum Therefore it is tempting to speculate that some of it is bound to systems that elaborate and secrete gastric juice and that parietal cells may transport it into the lumen of the gastric tubules with chloride

SUMMARY

(1) Concentrations of water nitrogen phosphorus chloride sodium potassium calcium and magnesium in mucosa and muscularis of stomach and colon are reported

(2) There is no significant statistical difference between the confidence limits of chloride in the antrum and fundus of stomach mucosa

(3) Sodium-chloride ratios of stomach and colon tissues approach the proportions of ultrafiltrate with exceptions as indicated

(4) Sodium and chloride are substantially more concentrated in stomach and colon smooth muscle than in skeletal muscle Potassium is less concentrated in muscularis than in skeletal muscle

(5) Calcium and magnesium concentrations in stomach and colon mucosa and muscularis are greater than in ultrafiltrate particularly in some colon mucosal tissue

(6) The ratio of the means of phosphorus and potassium in stomach mucosa is 0 5 in contrast to approaching unity in other tissues

(7) A concept is described which refers to the distribution of ions with respect to extra and intracellular phases of stomach and colon tissues

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DISCUSSION

DR FRANCIS D W LUKENS (Philadelphia) Has Dr Martin compared the uterine muscle with the smooth muscle of the intestine either by his own observations or from the literature?

DR LAY MARTIN (Closing) Dr Lukens there is a considerable number of reports on uterine musculature The ionic constitution of the uterus depends upon the state of esterus To a d gree it is similar to that observed in smooth muscle of the stomach

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At the end of the experiment the volume of fluid remaining in the chest was measured They found that the absorption of injected serum or isotonic saline was slow requiring 24 hours or more for complete removal

The original stimulus for the present study was the finding by Burke[3, 4, 5] that finely-divided lampblack and tubercle bacilli are transported from the *pleural cavity to the parasternal and the para aortic lymph nodes* and that exercise greatly accelerates this process

This investigation was undertaken to obtain information concerning the factors that regulate the formation and removal of pleural fluid in the unanaesthetized dog and in man

Methods

Trained unanaesthetized dogs were used Fine polyethylene catheters were introduced into one pleural space and into a superficial vein of a limb Approximately 8 ml/kg of sterile homologous heparinized plasma or serum was injected into the pleural cavity with a measured amount of T1824 Plasma and pleural fluid were sampled at appropriate intervals for dye estimation Protein in the pleural fluid was determined by a biuret method At the end of the experiment the volume of fluid remaining in the chest was measured by injecting 50 ml of saline and noting the dilution Plasma volume and dye disappearance rate for each dog were determined as a separate experiment These data permitted the absolute rates of entry and removal of fluid to be calculated A full account of the methods used will be published elsewhere

Results

For several hours after serum or stored plasma had been introduced into the pleural cavity the rate of fluid formation was abnormally high owing probably to the presence of the permeability increasing factor recently described in serum by Miles *et al*[6, 7] There was no such increase in the rate of removal In order that the experiment should be started under steady state conditions the plasma or serum was injected in the evening and the dye was introduced the next morning when the rates of formation and absorption were stable Fig 1 shows a typical experiment The apparent rise in fluid turnover during the first hour and a half is an artefact due to the time it takes for the dye stained fluid to permeate the pleural lymphatics In this experiment the rate of formation exceeded the rate of absorption but the converse was just as frequently found on the average formation nearly balanced absorption and the net volume change was small (less than 0 12 ml/kg hour) The turnover of fluid however was relatively large the mean value for both absorption and removal was of the order of 0 5 ml kg hour

WATER, SOLUTE AND CELL EXCHANGES IN THE DOG'S PLEURAL FLUID

By HUGH E. BURKE, M.D.,* AND (by invitation) E. B. STEWART, M.B., M.R.C.P.,† AND A. S. V. BURGEN, M.B., M.R.C.P.‡

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Introduction

Starling, during his classical studies of fluid exchange between blood and tissues, investigated the formation and removal of pleural fluid in anaesthetized dogs. He and Tubby[1] found that distilled water and other hypotonic solutions and dyes of low molecular weight such as methylene blue and indigo carmine, were rapidly removed from the thoracic cavity of the anaesthetized dog. Isotonic saline disappeared only very slowly *and hypertonic solutions of saline or glucose increased in volume.* On three occasions the fluid introduced into the pleural space was the animal's own defibrinated blood or serum, and in two of these more fluid was recovered at the end of six hours than had been administered. In all these experiments only the net change in the volume was measured, since the turnover of fluid could not be assessed. Starling and Tubby also observed that when a protein free solution was introduced into the pleural cavity it became within a few hours turbid or blood stained, and contained a good deal of protein.

A further advance was made by Courtice and Simmonds[2] who showed unequivocally that serum introduced into the pleural cavity of the cat was removed mainly or wholly by way of the lymphatics and that this removal was accelerated during the hyperventilation produced by CO_2 administration. They also studied the rate of removal of serum and isotonic saline in unanaesthetized rabbits over a period of one to two days. They introduced into the pleural cavity, together with the serum or isotonic saline, a known amount of the dye T1824, which forms a stable complex with albumin, and determined the rate at which the dye entered the blood

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‡ Professor of Physiology, McGill University.

This work was supported in part by the Blanche Hutchison Fund and a National Health Grant.

Protein and Cell Concentrations

The protein concentration of the pleural fluid 16–17 hours after the introduction of the serum averaged 83% of that in the plasma When fluid poor or rich in protein was introduced the protein concentration rose or fell towards this level

The cell concentration of the fluid rose and reached a steady level after 5–6 hours (Fig 2) For red cells this level was 100 000 to 150 000 cmm (about 2 to 3% of the peripheral blood count) but the white cell count reached 30 000 to 60 000/cmm which was considerably above the count in the peripheral blood The differential count in the pleural space was similar to that in the blood

The Effect of Hyperventilation and Anaesthesia

The hyperventilation induced in the dog by the inhalation of 3–10% CO_2 in room air was accompanied by a striking increase in the rate of fluid removal In the example shown in Fig 3 the rate of absorption was 0 7 ml/kg hour in the control period and rose to 3 2 ml kg hour while 10% CO_2 was being inhaled Following the return to breathing room air the rate of absorption fell slightly but remained high for the rest of the test period This after-effect was often seen more than 8 hours may be needed for return to the resting level The rate of fluid formation was little changed by CO_2 inhalation

The converse effect was seen when the respiration was depressed by intravenous sodium pentothal The rate of absorption fell to a very low level

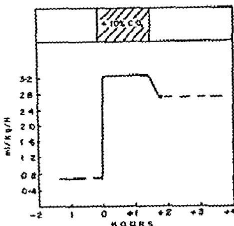


Fig 3 A typical experiment showing the effect on the rate of absorption of the inhalation of CO_2 The dog weighed 1 7 kg After a control period 10% CO_2 in air was inhaled by the dog during the period indicated

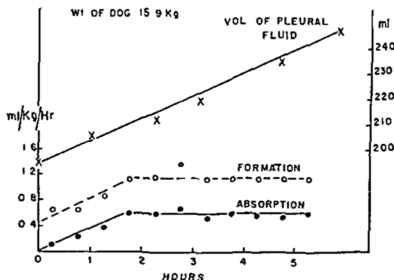


FIG 1 The rates of formation and absorption of pleural fluid in a resting unanesthetized dog 150 ml of homologous serum had been injected into the pleural cavity 17 hours before the start of the experiment More fluid was present at this time than originally injected The rate of fluid formation in this example exceeded the rate of absorption so that there was a steady rise in the volume of fluid present in the pleura

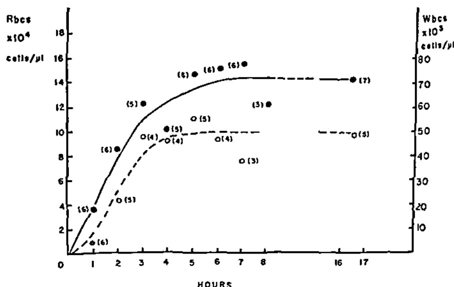


FIG 2 Concentration of red and white cells in the pleural fluid after injection of cell free serum The level of red and white cells reaches a peak after 5–6 hours There is little change after 16–17 hours

The Effect of Changes in Crystalloid Osmotic Pressure

Very rapid water shifts in or out of the pleural cavity can be produced by changing the total osmolyte concentration. Fig. 5 shows the effect of raising the Na concentration from 133 mEq/L to above 400 mEq/L by

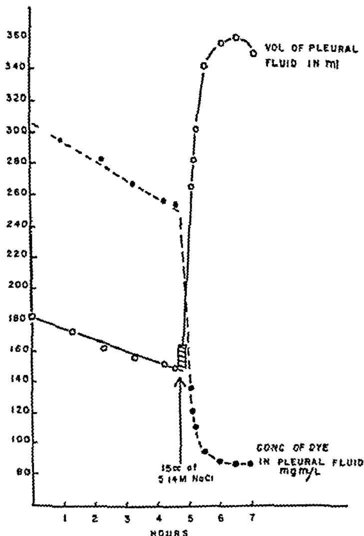


Fig 5 The effect of hypertonic solution. Increase in the pleural fluid volume and rapid dilution of dye occurred after the introduction of 15 ml of 5.14 M NaCl. The protein concentration fell from 5.5 g/100 ml to 2.2 g/100 ml

while the animal was unconscious and quickly returned to the resting level on recovery The rate of formation of fluid was unaltered

The Effect of Changes in Intrapleural Pressure

The mean intrapleural pressure was measured by connecting the catheter to a capacitance manometer When the mean pressure was raised by increasing the volume of fluid within the pleural space the formation of new fluid was slowed down or stopped altogether In the experiment illustrated in Fig 4 the formation of fluid was initially 1–1 5 ml/kg hour and the mean intrapleural pressure was −5 cms of water 394 ml of 0 85% NaCl were then introduced into the pleural space and the intrapleural pressure rose to +5 cms of water The formation of fluid ceased completely The rate of removal was increased a little by this change of pressure

The Effect of Histamine

The introduction of histamine in minute doses directly into the pleural fluid was followed by an increase of up to tenfold in the rate of fluid formation with only minor effects on the rate of removal No side effects were seen This action of histamine was completely prevented by the prior administration of a small dose of pyranisamine or chlorcyclizine

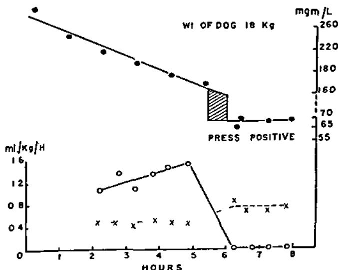


Fig 4 The effect of raising the mean intrapleural pressure In the control period the mean intrapleural pressure was −5 cm of water During the time shown by the cross hatched area 394 ml of 0 85% saline was introduced and the mean intrapleural pressure rose to +5 cm of water O—O Rate of Formation X—X Rate of Absorption ●—● Dye Concentration in Pleura

protein content means that the effective colloid osmotic pressure difference between plasma and pleural fluid must be less than 3 mm Hg It would not be expected therefore that colloid osmotic pressure gradients would have much effect on the rates of formation and absorption of the fluid This has indeed been found to be the case On the other hand far steeper gradients can easily be produced by alterations of crystalloid osmotic pressure and correspondingly large shifts of fluid are then observed In Fig 3 for example the initial osmotic gradient after the introduction of hypertonic saline was about 2×10^4 mm Hg or some 4 000 times the colloidal osmotic pressure gradient The pleural capillaries are thus set apart from ordinary tissue capillaries by their relatively high permeability to protein In the tissues colloidal osmotic pressure differential is a major factor regulating the formation and the removal of extravascular fluid but in the pleural cavity it has little part to play It seems likely that the pleural fluid is formed by bulk flow along a simple hydrostatic pressure gradient Since it ceases to be formed when the intrapleural pressure is raised to +5 cm of water the driving pressure in the capillaries must be low and it seems likely that the capillaries in question belong to the pulmonary rather than the bronchial circulation Once fluid has crossed the capillary wall into the pleural space no hydrostatic force is present to assist its return to the venous end of the capillaries It can only be removed by entering the lymphatics along which it is propelled by movements of the chest wall The sharp distinction between the process by which fluid is formed and the process by which it is removed is well illustrated by the effects of hyperventilation anaesthesia increased intrapleural pressure and histamine each of which acts selectively on one of the processes

The second feature of interest is the high white cell count in the pleural fluid After the injection of cell free serum white and red cells enter the fluid the white cells entering at a proportionately higher rate than the red cells Once the steady-state is reached the white cell count is some four to five times higher than the count in the peripheral blood whereas the red cell level in the pleural fluid at the same time is only 2–3% that in the peripheral blood The mode of entry of red blood cells is probably due to passive filtration but this cannot account for the large number of white cells It should be remembered that the rate of entry of cells shown in Fig 2 may be abnormally high because of the presence of the permeability increasing factors of stored serum [6, 7] which also give rise simultaneously to a large outpouring of fluid An attractive speculation is that some chemotropic substance is present in the fluid and may explain the high white cell count but there is no evidence for this The high white cell count was not due to infection as no dog was ever ill following these pro-

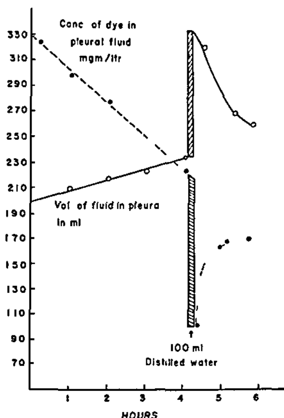


FIG 6 The effect of hypotonic solutions Rapid reconcentration of the dye in the pleura and fall in volume after the introduction of 100 ml of distilled water The protein concentration fell from a resting level of 5 g/100 ml to 3 g/100 ml and rose again to 4 2 g/100 ml

the injection of 15 ml of 5 14 M NaCl into the pleural fluid The volume *of pleural fluid rose within 30–45 minutes from 147 ml to 348 ml* Fig 6 shows the converse effect produced by the injection of distilled water with a rapid fall in volume and reconcentration of the dye in the pleural space

Discussion

The method described permits reliable measurement of slowly changing rates of pleural fluid formation and removal Rapid changes impose special difficulties and cannot at present be measured with any precision

The high protein concentration and the high white cell count of dog pleural fluid deserve comment The protein concentration was on the average 83% of the plasma protein level The fibrinogen content and the albumin globulin ratio were about the same as for the plasma The high

3 Burke H I The Role of Pleural Lymphatics in the Pathogenesis of Cold Abscesses of the Chest Wall and Paravertebral Abscesses J Thorac Surg 9 506 1940
4 Burke H I The Pathogenesis of Tuberculosis An Experimental Study Tr Am Clin and Clim Assoc 15 65 1953
5 Burke H I The Lymphatics Which Drain the Potential Space Between the Visceral and the Parietal Pleura (In preparation)
6 Miles A A and Wilhelm D I Enzyme Like Globulins From Serum Reproducing the Vascular Phenomenon of Inflammation I An Active Permeability Factor and Its Inhibitor in Guinea Pigs Serum Brit J Exp Path 36 71 1955
7 Wilhelm D I Miles A A and Mackay M I Enzyme Like Globulins From Serum Reproducing the Vascular Phenomenon of Inflammation II Isolation and Properties of Permeability Factor and Its Inhibitor Brit J Exp Path 36 82 1955

DISCUSSION

Dr Robert L Levy (New York) I would like to ask Dr Burke whether he has made any observations on varying the concentration of inhaled oxygen particularly increasing the percentage of oxygen

Dr John H Skavlem (Cincinnati) This is a beautiful demonstration of hormones in the normal pleural fluid and the normal pleura I was trying to apply this to the humans

It is to be remembered that the lymphatic flow in the pleura is altered considerably by conditions in the lung itself I stuck a few lantern slides in my pocket which I asked Dr Burke if he would mind if I showed illustrating the influence of certain conditions in the lung altering the pleural lymphatic flow

We know that the normal flow of lymph from the interior of the lung is toward the hilum except for a small area under the pleura in which the lymph flows toward the pleura

[Slide] Here we see a section of the pleura with the dilated lymphatics due to the fact that in the lung there has been scarring which directs more of the lymph flow toward the pleura under such conditions

In older individuals who have had a lot of pigment deposited in the interior of the lung in tuberculosis or in other changes which have brought about blockage in the lymphatics in the lung we may have more lymph flow diverted toward the pleura

[Slide] Here you see a valve at the junction of the septum and pleura opening toward the pleura and you see how markedly dilated the lymphatic in the pleura is

[Slide] Here is a slide showing pigmentation along the lymphatics in the pleura This pigment has been carried from the lung out into the pleura and deposited along the lymphatics

A point which Dr Burke made is how much more rapidly pigment is carried to the regional lymph nodes in an animal which is exercising

[Slide] We see this illustrated Here it shows pigment collected in the lymphoid tissue at the junction of the septum and the pleura showing how the pigment is collected in the lymphoid tissue This is particularly predominant where the septum joins the pleura

If you take a lung at autopsy in which there is considerable pigment deposited you can see the difference in the amount of pigment in the lung which immediately underlies the intercostal space and that which lies under the ribs In other words you can see clearly illustrated the point which Dr Burke has made that the pigment

cedures and though used repeatedly, no evidence of adhesions or past inflammation of the pleura was detected at post mortem in any of the animals These facts together with the effect of histamine in producing an increase in the rate of formation show the important role that the permeability of the capillaries plays in pleural fluid formation

There appear to be three main factors controlling pleural fluid formation 1) The hydrostatic pressure in the capillary, 2) The permeability of the capillary and 3) The negative intrapleural pressure

Finally it must be noted that the circulation of fluid through the pleura is quite substantial At rest approximately 25% of the plasma volume of the dog traverses the pleural space in 24 hours to be absorbed by the lymphatics New fluid from the pleural capillaries (as indicated by the dilution of the dye concentration in the pleural fluid) is added at a rate almost equal to the rate of removal so that the net changes in volume are relatively small

Summary

1 A method of measuring the turnover of pleural fluid in the unanaesthetized dog is described

2 Evidence for the existence of two independent balanced mechanisms for formation and absorption of fluid in the pleural cavity is presented and discussed

3 There is a substantial turnover of fluid in the pleural space representing about 25% of the dog s plasma volume in 24 hours

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7 Rapid movements of solutes and electrolytes occur under crystalloid osmotic pressure gradients

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nisms The main factors involved in the formation of pleural fluid are hydrostatic pressure relationships Once fluid is moved out of the capillaries it crosses the potential space and is absorbed by the lymphatics which are an independent valved system The rate of absorption is mainly influenced by respiratory movements This is in accord with the effect of movement on lymphatic flow elsewhere

It is interesting to hear Dr Lincoff's observation that air in the pleural space cuts short the course of pneumonia One can only speculate that the presence of air may have raised the intrapleural pressure and so reduced or cut off the formation of pleural fluid We have not as yet studied fluid transfer in a hydropneumothorax

DR HUGH I BURKE (Closing) Thank you very much Dr Skavlem for your beautiful demonstration of lymphatic channels in the pulmonary parenchyma and for your remarks concerning our studies We all I am sure are tremendously interested in the role of lymph transport in disease I wish that I could add something to knowledge of lymph flow within lungs that are the site of disease Only healthy dogs you will recall were used in the experiments on which we have reported today At present we are trying to get a few points concerning the lymphatics which drain the pleural space in health clearly established

I propose to tell you a short story about the way in which I became interested in lymph flow I shall be brief One day several years ago Dr Bray of Ray Brook asked me how our superintendent of nurses happened to get a chest wall abscess twenty five years after she had had pleurisy I found in a footnote in Cunningham's text book of anatomy a statement to the effect that Souligoux of France had observed lymph channels in pleuritic adhesions I secured a copy of Souligoux's thesis and discovered that it was questionable whether he had seen lymphatics in pleuritic adhesions I did a few simple experiments These showed that in guinea pigs lamp black is transported from the pleural space to certain lymph nodes before adhesions have time to develop

Concerning Dr Badger's question We—Dr Mankiewicz our bacteriologist and I—have carried out a number of experiments in which tubercle bacilli were introduced into the pleural space of vaccinated (Mantoux positive) guinea pigs Some very interesting things have come from these experiments as those of you who heard the paper that I read at this year's Meeting of the American Trudeau Society know We have not as yet made an attempt to follow the pathogenesis of intrapleurally induced tuberculosis in animals that are being given chemotherapy

Only a few investigators appear to have introduced bacteria into the pleural space of experimental animals No one except ourselves as far as I can learn has followed for a long time animals that have been given an intrapleural injection of tubercle bacilli In the course of a study of the defensive mechanisms of the mediastinum Cooray of England introduced tubercle bacilli into the pleural spaces of guinea pigs He found that these micro organisms congregate in Kampmeier's foci in the retrocardiac folds soon after they are injected He noted that tubercle bacilli which lodge in these sites multiply and in a matter of days are carried on into the mediastinal tissues and by way of the blood stream to distant parts of the body

Some one—at the moment I cannot recall who—gave guinea pigs an intratracheal injection of streptococci in suspension in broth and found that in a matter of minutes they were carried to among other places the pleural space

These experiments clearly indicate it seems to me that investigators other than ourselves are interested in the sites to which bacteria introduced into the chest are conveyed

I have no precise data to use in my reply to your question Dr Woodward An amusing story will serve to illustrate our present views with respect to the role of

is mobilized in the lung which has the most expansion in the interspaces while in that under the ribs the pigment will remain in the area You can see that plainly on the growth specimen The pigment is carried down into the abdomen (the point Dr Burke has made on previous presentations) to the lymph nodes of the abdomen This is carried by lymphatics of the pleura extending in the ligamentum pulmonale then down into the abdomen

Dr Theodore L Badger (Boston) I want to compliment Dr Burke on his really very ingenious and interesting demonstration of the mechanical absorption of the fluid from the pleura I want to ask him if he has applied this to bacterial infections of various sorts particularly to tubercle bacilli and both with and without chemo therapy

Dr Theodore E Woodward (Baltimore) I wonder whether Dr Burke and his group have any information as to the effect of corticoids on the transport of tracer substances in their interesting animals

Dr Theodore J Abernethy (Washington D C) I would like to ask Dr Burke if he has used morphine in any of his experiments in dogs which might be expected to slow the respiratory rate I should also like to ask whether he can postulate that morphine might be contra indicated in an individual with a pleural effusion because of its effect of slowing the respiratory rate

Dr Francis C Wood (Philadelphia) In these beautiful experiments it has been demonstrated that certain changes in the respiratory rate change the rate of ab sorption You also said that formation and absorption stayed quite close to each other I wonder if there is any thought in your mind that it might be primarily a change in the rate of formation which produced the change in the rate of absorption

Dr Maurice Charles Pincoffs (Baltimore) The effect of pressure changes in the pleural cavity during exercise on the transport of pigmented material from within the lung to the pleural surface has been referred to by one of the discussants of this interesting paper

A possible further example of this relationship may be recalled by many of you I refer to the therapeutic use of pneumothorax in lobar pneumonia This had a brief vogue just prior to the use of sulfonamides Observations made at that time showed that the injection of air into the pleural cavity in lobar pneumonia would often abruptly alter the course of the disease bringing the temperature down in a crisis like manner and lessening in other ways the evidences of toxemia

Such effects might be explained by assuming that whereas exercise accelerates the transport of material from the interior to the surface of the lung the reverse occurs when pneumothorax has placed the lung at rest so that in pneumonia the toxic products of the inflammation reach less readily the lymphatics of the pleural surface

Dr P B Stewart (Closing) I would like to answer the questions which have a bearing on the physiological studies and pass on the others to Dr Burke In answer to Dr Levy we have done no experiments with variations in inspired oxygen ten sions

In reply to Dr Woodward the effect of corticoids in absorption of solutes and electrolytes in the pleural space has not been investigated

Dr Abernethy s question is a difficult one to answer and we have given the matter much thought Whether the fall in the rate of absorption with pentothal anaesthesia is related to unconsciousness or whether it can be reproduced by simply depressing the respiratory rate with morphine has been considered but not tested because of difficulties in using morphine in unanaesthetized dogs We hope to use other methods of depressing respiration but have not done so as yet

We think that absorption and formation of pleural fluid are independent mecha

HIGH PROTEIN EDEMA DUE TO DIFFUSE ABNORMALITY OF CAPILLARY PERMEABILITY

By KENDALL EMERSON, Jr., M.D. AND S. HOWARD ARMSTRONG, Jr., M.D.

BOSTON AND CHICAGO

At the meeting of the Clinical and Climatological Association one year ago Dr. Elliot Newman reported a case of generalized edema of obscure origin.[1] He presented evidence to suggest that the edema was due primarily to a disturbance in the reciprocal handling of sodium and potassium by the kidney.

This year we wish to present in further detail the patient whom we mentioned in the discussion of Doctor Newman's paper and who exhibits what we believe is a different and hitherto undescribed cause for generalized edema. The patient (PBBH 5A246) is now a 36-year old registered *nurse who was first admitted to the Peter Bent Brigham Hospital December* 10, 1945 on the Service of Dr. James P. O'Hare with the complaint of generalized edema. Her symptoms began insidiously 5½ months prior to admission with swelling of the ankles, gradually extending over the next two months to involve her legs, thighs, lower back and abdomen. Three months before admission facial edema first appeared followed by a sensation of tightness in the chest and increasingly severe exertional dyspnea. Except for frequent upper respiratory infections and moderately severe varicose veins the patient's past health had always been excellent. Four years prior to admission she had developed a sulfanilamide rash following treatment of eczema with an ointment containing this drug. She had always been obese but during the four months prior to her illness she had reduced her weight from 224 to 187 pounds by restriction of caloric intake.

Physical examination at the time of admission revealed normal vital signs with a blood pressure of 122/82. The patient was a well developed obese young white female with moderate orthopnea but no cyanosis or venous engorgement. The face and eyelids were edematous and there was massive edema of the lower extremities extending upward as far as the

From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston, Massachusetts, and the Hektoen Institute for Medical Research of the Cook County Hospital,† and the Department of Medicine of the University of Illinois.

Continuation of studies on osmotic pressure and edema has been carried out under a grant from the U. S. Public Health Service.

† One of us (S. H. A., Jr.) is indebted to the Drs. Leonard H. and Louis D. Wiesman Medical Research Foundation for the backing of the studies of plasma proteins as related to disease mechanisms at the Hektoen Institute.

adreno corticoid hormones in experiments of the kind that we have been considering Dr Max Lurie of Philadelphia questioned our interpretation of our experiments with guinea pigs when first he heard about them He said he thought that we were frightening the guinea pigs when we put them in a noisy treadmill that as a result they secreted large amounts of adreno corticoid hormones and that the latter were responsible for our so-called exercise effects We took Dr Lurie s criticism in good part A year ago we were able to give him the results of the experiment in which guinea pigs were exposed for short periods to a gas mixture containing 1% CO_2 The guinea pigs as you can appreciate could not see or hear the gas mixture to which they were exposed Dr Lurie s response was Surely I was not foolish enough to think that adreno corticoid hormones were responsible for the effects you were finding in animals that were made to walk at a quick pace in a treadmill

With respect to your question concerning rates of formation and absorption of fluid Dr Wood Two or three years ago when wondering about the fluid that permits the visceral pleura and the parietal pleura to glide smoothly the one over the other under various conditions I came to the conclusion that if a person runs a race the amount of fluid probably increases Enough fluid to keep both visceral pleura and parietal pleura moist obviously must be present I decided that if this is true some means for removing or absorbing excess fluid must also be present My thinking in this connection was probably influenced by the fact that a Japanese worker is reported to have found accumulations of fluid in excess of usual quantities in the pleural spaces of soldiers immediately following strenuous exercise At the moment I have nothing else to add to Dr Stewart s reply to your question Dr Wood

Finally a word or two concerning your query Dr Pincoffs An experiment which a Japanese investigator carried out some years ago seems to me to have a bearing on your very interesting observation This worker found that if he allowed rabbits to inhale finely divided lamp black kept half of them as controls and promptly induced a unilateral pneumothorax in the other half the lamp black that the latter inhaled remained in the alveoli The lamp black in other words was not transported from the pulmonary parenchyma to the tracheobronchial lymph nodes as was the case in the control animals

We as is obvious still have much to learn about many things

TABLE I

Laboratory Data

Urine
- Protein 0-0 23 gms /I
- Sp gr 1010 1027
- pH 5 0-7.5
- Sediment 0 many hyaline casts

Blood
- Hinton negative
- Hematocrit 44 Sed rate ?
- Serum protein 4 4 5 5 gms %
- Albumin 2 8-3.3 gms %
- Cholesterol 336-441 mgs %
- BUN ?-14 mgs %
- Ca 4 5-5 0 m eq /L PO 1 3 mM/l
- Na K and CO normal

Miscellaneous
- PPD negative
- Congo red 24% removal
- 17 ketosteroids 8 6 mgs /24 hours
- 17 hydroxysteroids 4 3 mgs / 4 hours
- Glucose tolerance test normal
- B M R I BI and RaI uptake normal
- ADH assay normal

Kidneys
- I V P normal
- C_{IN} 115 cc /minute
- C_{PAH} 4?? cc /minute
- Tm_{PAH} ?? 4 mgs /minute
- Filt Fract 0 25
- Cl_{L} 58%
- PSP 0% in 2 hours

Liver
- BSP 5% retention
- Bilirubin .3? mgs %
- Alk P tase 3 0 G U
- Thymol 2 6 MachLachlan Units

Heart
- X ray normal
- EKG low EMF
- V P 1?0-190
- C T 1 second

TABLE II

Tiselius Pattern

Protein	Serum	Tissue Fluid
	gm	gm %
Total protein	5 .	1 90
Albumin	2 08	1 35
Alpha 1 globulin	30	08
Alpha 2 globulin	8	1?
Beta globulin	99	16
Fibrinogen	68	0
Gamma globulin	36	?1

This value was 3 0 by ammonium sulphate fractionation

is the serum of an adult chronic glomerulonephritic after a remission of the nephrotic syndrome Both sera have in common a very low gamma globulin However the characteristic elevation of alpha and beta associated with the hyperlipemia of the nephrotic syndrome is not seen in our patient nor is there a comparable elevation in fibrinogen

A list of some of the types of therapy employed to combat the edema in this patient is given in Table III The most successful of these has been the cation exchange resins which she has been receiving continuously since

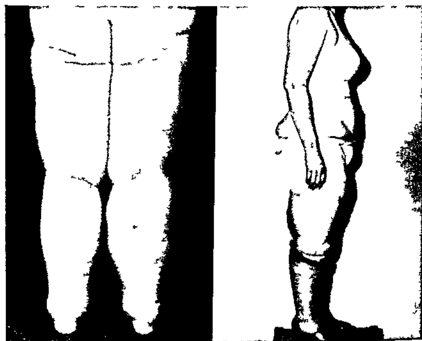


FIG. 1. Appearance of patient M. I. in 1947 left and 1955 right after five years of cation exchange resin therapy

lower thorax (Figure 1). Respiratory excursions were limited and both lung bases showed dullness up to the scapulae. The heart was not enlarged and the sounds were normal. A soft blowing Grade I systolic murmur was audible at both base and apex. Shifting dullness and a fluid wave were present in the abdomen and the liver descended two fingerbreadths on inspiration. The spleen was not palpable and except for varicose veins the physical examination was otherwise not remarkable.

X ray of the chest revealed bilateral pleural fluid freely moveable without cardiac enlargement. A biopsy of the skin and subcutaneous tissues of the abdomen revealed slight swelling of the endothelium of occasional vascular channels and a small amount of chronic inflammatory cell infiltration around some vessels but nothing to suggest fibrinoid changes.

Some pertinent laboratory data together with renal clearance studies are presented in Table I. The bottom schlieren diagram in Figure 2 illustrates the electrophoretic distribution of the plasma proteins as detailed in the first column of Table II.* For comparison the top schlieren diagram

* This electrophoretic diagram was made sometime after the courses of albumin therapy subsequently to be described.

never encountered edema fluid protein levels greater than 1 gm % and usually the level is below 0 5 gm %. Massive parenteral albumin therapy in these conditions will rarely elevate the edema fluid protein level to above 1 gm %)

For our patient M L we have one refractometrically determined protein level in edema fluid before albumin therapy. This was 0 8 gms % (identical to the level noted by Newman and coworkers in his patient[9]) We have many subsequent observations of protein levels in edema fluid during and following albumin therapy of which the highest values were well over 3 gms % (during and immediately after intensive parenteral albumin) and the mean value about 2 gms % (at long periods after parenteral albumin)

The electrophoretic distribution (classical Tiselius technique) of the proteins in one of the latter edema fluid collections is detailed in the second column of Table II. For contrast in Figure 3 are illustrated the electrophoretic distributions (paper electrophoresis technique) of serum and edema fluid simultaneously obtained from a very recently observed subject on the wards of Cook County Hospital suffering from a progressively fatal condition combining features of dermatomyositis with erythema multiforme. It will be noted that the ratio of albumin to gamma globulin in M L s edema fluid is 9/1 while in subject D J it is 1 5/1. The comparable plasma ratios are 5/1 for M L and 1 1/1 for D J. Thus while the extraordinarily high total protein level (4 2 gms %) in the edema fluid of D J

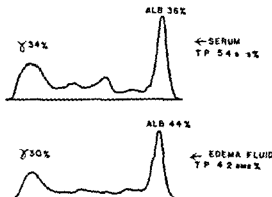


FIG 3 (For description see text)

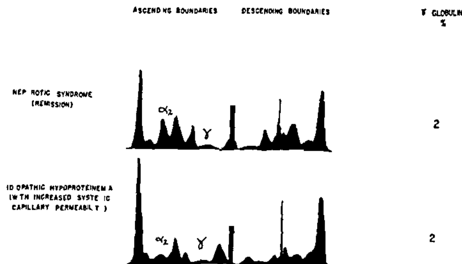


Fig 2 (For description see text)

TABLE III

Attempts at Diuresis

Digitalis	Induction of Alkalosis
Ammonium Chloride	ACTH
Mercurials	Cortisone
Urea	12% Dextran
Thyroid	Typhoid Vaccine
Parathyroid	Diamox
Salt poor Human Albumin	Di amino Uracil (Mictine)
Salt poor Human Globulin	Cation Exchange Resins
Mannitol	

1949 with sufficient control of edema to allow her to resume her occupation of nursing

During the years 1946 to 1949 repeated chest taps and drainage of the subcutaneous fluid from her legs by Southey tubes were required to keep her comfortable As much as 5000 cc of subcutaneous fluid could be removed in 24 hours by this method The ease and rapidity with which large quantities of this fluid could be obtained makes unlikely any contamination with significant amounts of serum

Analysis of this fluid consistently revealed protein content exceeding the range usually associated with nephritic nephrotic cardiac and nutritional edema (In our own experience with the latter conditions we have

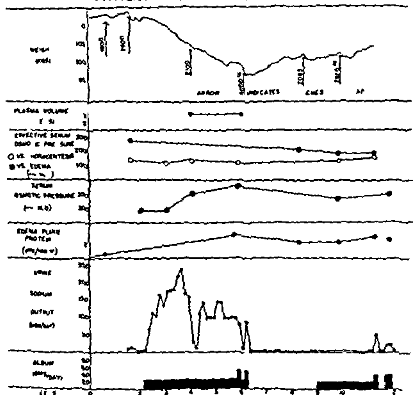


Fig 4 (For description see text)

taneously obtained edema and thoracentesis fluids (thus paralleling in vitro the in vivo situation) we obtained results designated *effective osmotic pressures*[2] which far from restoration to normal showed for edema fluid a decline and for thoracentesis fluid no significant change (Figure 4 *third and fourth sections from the top*) On the right hand side of Figure 5 is illustrated the contrasting behavior of serum and effective osmotic pressures for patient B M The much smaller total dose of albumin increased serum osmotic pressure from the very low value of some 100 mm of water to a normal value of over 400 mm of water when measured against isotonic saline When measured against simultaneously obtained edema fluid the increase in effective osmotic pressure was almost as great

Again on the left side of Figure 5 is illustrated serum and *effective* osmotic pressure changes for a subject (M P) with nephrotic syndrome

indicates a pathological increase in capillary permeability even greater than that in patient M I albumins (molecular weight 69 000) and gamma globulins (molecular weight about 160 000) pass through the capillary walls in amounts about proportional to plasma concentrations The extra ordinary difference in edema gamma globulin levels between these two patients reflects the abnormally high plasma gamma globulins in D J and the abnormally low plasma gamma globulins in M I respectively

The most significant observations on the movement of protein from plasma to edema fluid were made during M I s intensive intravenous salt poor albumin therapy During a preliminary control period, the patient s weight was stable at about 112 kilos On an oral sodium intake of less than 35 meq a day the patient s 24 hour urinary sodium output was less than 10 meq When 25 grams of albumin were injected intravenously daily there began a simultaneous diuresis of salt and water such that by the tenth day of therapy the 24 hour sodium output was 240 meq and the patient s total weight loss was approximately 10 kilos In view of the failures detailed in Table III this initial result was gratifying alike to the patient and to her physicians and is graphically presented on the top next to bottom and bottom sections of Figure 4 (weeks 2 to 4)

While at this point the patient still had plenty of edema yet to lo e two further weeks of intravenous albumin at this dosage was associated with a progressive diminution of this diuresis of salt and water After some four weeks of therapy increasing the daily dose to 50 grams a day failed to restore the diuresis to the previously observed maximum On cessation of albumin at the end of a month urinary sodium output fell to control levels and weight began to increase (Figure 4 weeks 6 to 9) Some three weeks later the resumption of albumin therapy failed to induce any further significant diuresis of salt and water and weight continued up a result as unsatisfactory to the physicians as it was to the patient

For this sequence of events was entirely different from those we were seeing at the same time in another subject B M who suffered from an idopathic hypoproteinemia While by no means as edematous as M I a much shorter intravenous course of salt poor albumin in B M resulted in diuresis of salt and water until the edema had wholly disappeared al though the sodium intake in the latter subject was not as restricted

The mo t *striking laboratory difference observed during the periods* of albumin between these two subjects were in the response of their *effective* serum colloid o motic pressures to albumin therapy

As shown in the fourth section from the top of Figure 4 the first course of albumin therapy restored M I s serum osmotic pressure as *measured against isotonic saline* to a normal value of some 370 mm of water When however we measured the osmotic pressures of serum against simul

TABLE IV

Colloidal Osmotic Pressure of Plasma and Extracellular Fluid (E.C.F.)

	Total Protein (C)		Albumin (A)		Osmotic Pressure C(0.59A + 2.14)		Effective Osmotic Gradient cm. H₂O	Hydrostatic Pressure	
	Plasma gm. %	E.C.F. gms. %	Plasma gms. %	E.C.F. gm. %	Plasma cm. H₂O	E.C.F. cm. H₂O		Capillary cm. H₂O	Tissue cm. H₂O
	(1)	(2)	(3)	(4)	(5)	(6)	(5−6) = (7)	(8)	(8 − 7)
Average normal values	6.0	0.[illegible]	4.0	0.[illegible]	26.00	1.[illegible]	24.[illegible]	[illegible]5.00*	3.[illegible]5
Patient M.L.									
Before I.V. albumin	5.3	[illegible].1	3.5	1.1	[illegible]	4.[illegible]0	18.00	28.00	10.00
After I.V. albumin 20 gms./d. ad 10	6.7	3.4	4.3	1.3	31.36	9.89	[illegible]1.4	28.00	6.53

* Capillary pressure is assumed normal.

ments of osmotic pressure are greatly preferable to calculations from Howe or electrophoretic data.

The familiar Starling's law states in essence that fluid will flow from capillaries to tissue spaces until the back hydrostatic pressure created by the distention of tissue spaces equals the *net difference* between the capillary hydrostatic pressure and the *effective* osmotic pressure between serum and tissue fluid.

Such net differences for patient M.L. (estimated from an assumed normal capillary pressure and a calculated effective osmotic pressure) are given in the last column of Table IV. These figures would make it seem that in the first two weeks of albumin therapy the diuresis was associated with a diminution of tissue hydrostatic pressure.

If however we substitute direct effective osmotic pressure measurements no such diminution is implied.

In any case, whether we use the calculated or directly measured values the fact remains that the highly abnormal *net difference* between effective osmotic and normal capillary hydrostatic pressures was certainly not brought back to the normal range by parenteral albumin in M.L. and was readily brought back in B.M. (Figure 5, right). A tentative interpretation for M.L. might be formulated thus:

During the first few days of albumin administration in our patient she showed a moderate diuresis and weight loss as would be expected from the rise in effective osmotic gradient and corresponding drop in tissue hydrostatic pressure. This diuresis ceased, however, in spite of the continued administration of albumin and the persistence of extensive edema

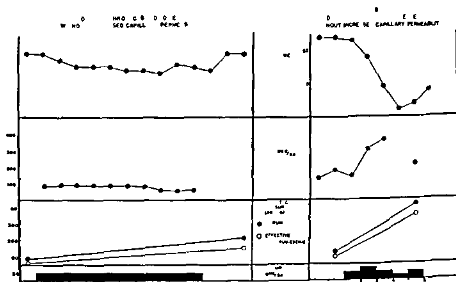


Fig. 5. (For description see text.)

edema under albumin therapy. Restoration of either measurement to normal is not accomplished but increases in serum and effective osmotic pressures are essentially parallel.

The reason for the opposite movements of serum and effective osmotic pressures is apparent from the increase of M. L.'s edema fluid protein as shown in the fifth section from the top of Figure 4. The maximum of 3.4 gms. % is 2 gms. % higher than we have ever encountered in cardiac, nephrotic, or cirrhotic edema fluid under albumin therapy.

In Table IV we have osmotic pressures as calculated from the Howe albumin globulin ratios according to the formula of Wells, Youmans and Miller[3] and expressed as cm. of water. The direct measurements of Figures 4 and 5 are expressed as mm. of water. Here we note that the *calculated* osmotic pressures for both serum and edema fluid were about 50–80 mm. lower than our direct measurements. This discrepancy is consistent in sign and approximate magnitude with the discrepancy one of us has more recently reported between osmotic pressures and calculated osmotic pressures in the nephrotic syndrome. This discrepancy only partially cancels out when *effective* osmotic pressure is estimated. Thus direct measurements against edema fluid yielded results from 30–60 mm. lower than the calculations.

These discrepancies emphasize the point we have emphasized elsewhere for valid correlation with the clinical sequences of edema, direct measure

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	Total Protein (C)		Albumin (A)		Osmotic Pressure C(0 59A + 2 14)		Effective Osmotic Gradient cm H₂O	Hydrostatic Pres	
	Plasma gms %	E C F gms %	Plasma gms %	E C F gms %	Plasma cm H₂O	E C F cm H₂O		Capillary cm H₂O	Tissue cm H₂O
	(1)	(2)	(3)	(4)	(5)	(6)	(5−6) = (7)	(8)	(8−7)
Average normal values	6 0	0 7	4 0	0 5	26 00	1 75	24 25	28 00	3 75
Patient M L									
Before I V albumin	5 3	2 1	3 5	1 1	22 50	4 50	18 00	28 00	10 00
After I V albumin 50 gms /d ad 10	6 [illegible]	3 4	4 3	1 3	31 36	9 89	21 47	28 00	6 53

Capillary pressure is assumed normal

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In any case whether we use the calculated or directly measured values the fact remains that the highly abnormal *net difference* between effective osmotic and normal capillary hydrostatic pressures was certainly not brought back to the normal range by parenteral albumin in M L and was readily brought back in B M (Figure 5 right) A tentative interpretation for M L might be formulated thus

During the first few days of albumin administration in our patient she showed a moderate diuresis and weight loss as would be expected from the rise in effective osmotic gradient and corresponding drop in tissue hydrostatic pressure This diuresis soon ceased however in spite of the continued administration of albumin and the persistence of extensive edema

Apparently when the serum proteins rose to normal the further administration of albumin resulted in the loss of more of it into the tissue spaces and the consequent failure of any further rise in the effective osmotic pressure of the blood Eventually a new equilibrium was reached between blood and tissue hydrostatic pressures at a still abnormally high level

Attractive as this tentative interpretation may be as stated it obviously cannot be extended to cover the response of other types of clinical edema to intravenous albumin therapy

Thus it has long been known that when albumin therapy effects a diuresis in a nephrotic it does so without any long term[4] or great immediate[4] rise in serum colloid osmotic pressure In such nephrotics who respond to albumin a transitory diuresis of salt and water follow shortly after the increase in plasma volume that the injected albumin brings about and maintains for a period of some hours

In Figure 6 are plotted hourly urine volume and sodium outputs against serum colloid osmotic pressures total proteins and hematocrits for the periods before and immediately after intravenous injection of 50 gms of salt poor albumin In the experiment on the left of Figure 6 the resultant drop in hematocrit indicates a rapid increase in plasma volume and is associated with a rapid rise of sodium output from below 2 to 11 meq per hour This diuresis is as transitory as those we have seen under the same conditions in the nephrotic syndrome sodium output has returned

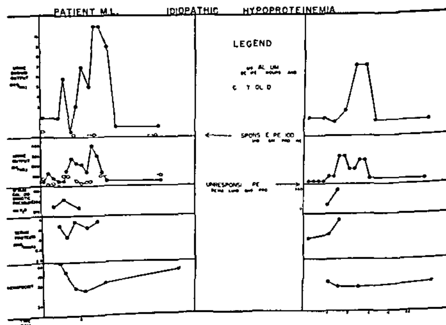


Fig 6 (For description see text)

to the base line before the hematocrit has returned to normal. Note that the injection results in no significant increase in serum osmotic pressure: the injected albumin immediately sucks water from interstitial fluid to plasma. This we have called an iso-osmotic albumin injection.

Now the experiment on the left of Figure 6 was carried out at a time just before the effect of albumin therapy on M.L.'s weight curve had completely disappeared (Figure 4, week 6). On the left of Figure 6 is plotted a comparable experiment when M.L.'s weight was rising despite daily albumin (Figure 4, end of week 2). Here we see a modest increase in osmotic pressure and a much less drop in hematocrit following albumin injection. The resultant diuresis of sodium is very much less than in the previous experiment.

It is of interest to compare the right side of Figure 6 with Figure 7.

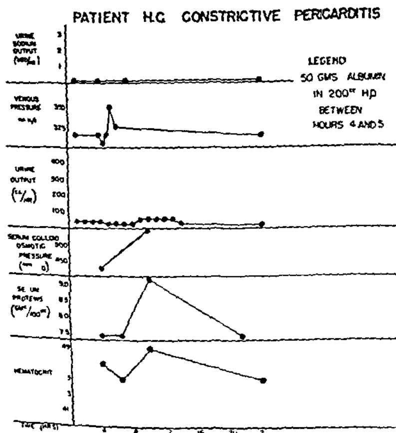


Fig. 7. (For description see text.)

Apparently when the serum proteins rose to normal, the further administration of albumin resulted in the loss of more of it into the tissue spaces and the consequent failure of any further rise in the effective osmotic pressure of the blood. Eventually a new equilibrium was reached between blood and tissue hydrostatic pressures at a still abnormally high level.

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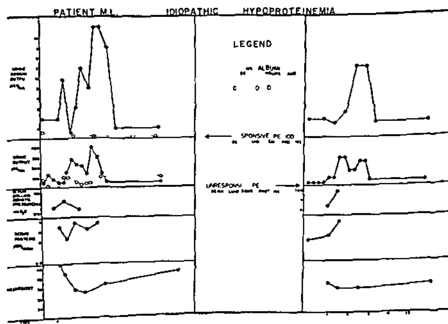


FIG. 6. (For description see text.)

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DISCUSSION

Dr Henry M Thomas Jr (Baltimore) I would like to ask a question In the case of a 51 year old man who would seem to have clear-cut glomerular nephritis with nephrotic syndrome and with hypertension blood pressure 200/100 with arteriosclerotic changes and with reduced renal function with normal serum proteins but with anasarca and with high protein (largely albumin) in the fluids but with anemia in whom the treatment on account of his nephrosis was low protein diet low salt diet cobalt and iron by mouth and (with caution) transfusion with washed red blood cells the diuresis seemed to start after the introduction of the red blood corpuscles which had been thought to be contraindicated by some of us who were taking care of this patient

Following this the nitrogen retention diminished and returned almost to normal He has been without ascites since last April or May he came in April I cannot be too accurate but under Dr Frederick Barnes who was very much interested in this case he had electrophoretic studies on sera thoracic and abdominal fluid and urine which I think were in the nature of yours Is this one of the group you are describing? Dr Barnes has found a number of cases with ascitic fluid or pleural fluid which had protein in the neighborhood of one to three grams or a little higher

Dr Robert L Levy (New York) I wonder whether Dr Emerson and Dr Armstrong would care to comment on the nature of this capillary permeability What is the mechanism involved

Dr John P Merrill (Boston) I would like to ask whether there was any association between the onset of diuresis and increase in cardiac output I ask this because of an observation we made at one time on a patient with cirrhosis when we attempted to effect an osmotic diuresis by glucose

We did this and measured cardiac output for another reason We found he had a maximum sodium diuresis which had not been associated previously with osmotic

which plots a comparable experiment in a patient with anasarca due to chronic constrictive pericarditis The osmotic pressure of serum rises precipitously the venous pressure rises almost as precipitously After a brief initial drop the hematocrit does not show enough change to reflect a significant increase in plasma volume

This type of response we have called an *isovolumetric* albumin injection Characteristic of all cardiac decompensations we have studied [8] we believe it reflects the hydrodynamic situation wherein elevated venous pressure and fixed cardiac output does not permit the albumin to suck significant amounts of fluid back into the circulation As illustrated in the top section of Figure 7 even a transitory diuresis of sodium and water is not seen after isovolumetric injections

Turning again to Figure 6 these considerations suggest that M L's initial iso osmotic response to intravenous albumin resulted in the transitory diuresis seen in the nephrotic or in nutritional edema but as the albumin in increasing quantity accumulated in her interstitial fluid her response became more isovolumetric In the shift from iso osmotic to isovolumetric responses the increasing osmotic pressure of edema fluid plays an analogous role to the elevated venous pressure in cardiac edemas

Further reflection indicates that while this is as far as we can go from the evidence at hand this description of mechanism leaves many things unexplained Thus when we did these determinations the flame photometer was new and aldosterone unheard of Subsequently we have noted that after *isovolumetric* albumin administrations in patients with fixed cardiac outputs brief potassium diureses ensue Perhaps in this finding a speculative bridge might be fashioned between our M I and Dr Newman s H H But we cannot go beyond speculation for we have no potassium outputs on M L during the experimental period Thus fuller elucidation must await simultaneous measurement of circulatory osmotic and the newer endocrine factors in future cases of this sort

Summary

We have reported a patient with idiopathic edema' who has been under clinical observation of one of us for over eight years and intensive experimental observation by both of us over a period of months during albumin therapy This subject differed from other idiopathic hypoproteinemic edemas we have studied in showing an abnormal permeability of peripheral capillaries to injected salt poor albumin Sequential direct measurements of effective osmotic pressures before during and after albumin administration are discussed in partial elucidation of the mechanism of this edema

STUDIES OF PANTOTHENIC ACID METABOLISM

By William B. Bean, M.D., and (by invitation) Robert Lubin and Kate Daum

With the technical assistance of James T. Bradbury, Ruth Gunning, Joseph I. Routh and I. Chu Tung

Iowa City

Introduction

My first experience with the problem of differing pharmacologic effects produced by chemical compounds with closely related molecular structure was reported in a study of the vasodilating capacity of nicotinic acid and related pyridine chemicals.[1] Several of the compounds we tested were mildly toxic. Woolley[2,3] demonstrated the harmful effects of 3-amino pyridine in experimental animals. The concept of molecular antagonists is that kindred chemical compounds compete for space on the surface of protein enzymes. If active compounds got priority, enzyme activity progressed naturally. If the available places are all taken by compounds which preempt surface space but have no active portion free, enzyme action halts. An early application to clinical problems was Woods'[4] observation of the antagonism by paraaminobenzoic acid of sulfanilamide in inhibiting bacterial growth. Reasoning by analogy, I tried to find compounds which by slowing or stopping the action of B-complex vitamins might give a clue to early and single vitamin deficiencies. Pyridine-3 sulfonic acid, which bears the same relation to nicotinic acid that sulfonilamide bears to PABA, was given to a number of patients with pellagra. No harmful effects occurred but the studies were not adequate to show whether the principle was wrong, the material inert or not given in adequate amounts or time. Later the soundness of the idea was demonstrated by the development of folic acid antagonists and the use of pyridoxine antagonists to produce human pyridoxine deficiency.[5]

In spite of the fact that pantothenic acid was established as essential for growth and health of experimental animals and certain lower organisms, nothing was known of its possible role in human nutrition and metabolism when we undertook our studies. The increasing importance of coenzyme A in many important metabolic and enzymatic actions was being unfolded.

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Supported by the Medical Department Trust Fund and grants from the National Vitamin Foundation, The Nutrition Foundation and the Burroughs Wellcome Co.

Died December 30, 19[illegible]

diuresis but was in this individual associated with a marked increase in cardiac output

DR S HOWARD ARMSTRONG (Chicago) In answering Dr Levy one of the troubles in implicating an allergic mechanism is that ACTH has no effect on the transudation of albumin in M L while it does cut down protein transudation in other allergic edemas we have seen This of course by no means rules out allergy

In some of the edemas which have been in the borderline range which Dr Thomas has discussed we had one or two patients very much like his and encountered comparable therapeutic responses

However the few borderline cardiac decompensations who have responded to *transfusion of albumin all have had a sudden blood volume increase rapidly induced* of about a liter This of course is reminiscent of the old Caughey test Dr Levy used to have us do except that you hold your increase in plasma longer

In answer to Dr Merrill s question I think he put his finger exactly on the phenomena we have been working on which have led to the hypothesis that the sudden increase in plasma volume starts an increase cardiac output this leads to the transitory diuresis of salt and water we have described

In certain nephrotics we have carried out simultaneous studies of both cardiac output and inulin and PAH clearance during albumin injection Time is too short to report these

The only reason the cardiac output is not the whole story is this Dr Merrill We studied as controls some patients who had good heart function and had edema for various other reasons We found patients who would have an excellent increase in cardiac index (say two or three) and still would have a negligible sodium transitory diuresis immediately following albumin I have in mind particularly one or two patients with generalized carcinoma but without Chiari s syndrome in other words no evidence of vena caval block That is why we strongly feel that there is a basic hormonal pattern on which these other phenomena are superimposed

DR KENDALL EMERSON JR (Closing) In answer to Doctor Thomas question concerning the beneficial effect of transfusion in a patient with chronic glomerulonephritis and anemia I suspect this is due more to the improvement in cardiac function and glomerular filtration rate rather than to a decrease in capillary permeability or elevation of serum osmotic pressure It might however improve capillary function by diminishing anemia *and consequent anoxia rather than by its physicochemical* effect on osmotic pressure

The nature of this condition which Doctor Levy inquires about is certainly mysterious to us We have done skin and muscle biopsies of this girl which show nonspecific changes There is a little perivascular inflammation in some areas and a little swelling of the endothelium of the capillaries It is not specific for any collagen disease or any other condition we know of The fact that she did have a sulfanilamide rash makes us think this might be in some manner related to a hypersensitivity state but it is not like anything we have seen before either clinically or pathologically It does not involve the kidneys and it has been completely unchanging and nonprogressive in the ten years we have followed this patient So thus far we have no explanation of the pathological or etiological mechanism which goes on here

employing a general hospital diet. Period II was to test the adequacy of the formula with mineral and vitamin supplements and the effects of intubation since the formula was intolerable by mouth. Period III was designed to see whether the deficient diet without the antagonist might induce changes in two weeks. Each of these periods in plan and in fact was two weeks long. Period IV with the deficient diet plus 500 mg of omega methylpantothenic acid was planned for four weeks. At the end of this time we extended it for one week because the clinical state of the subjects suggested that they had not reached a danger period. Their symptoms of illness were not as striking as those in the earlier study after four weeks of deficiency. Because 10 weeks is about the limit of endurance in taking the tubes, the planned recovery Period V with the formula plus pantothenic acid but without the antagonist was reduced from two weeks to a single week. During this week the general condition of one subject improved whereas the other had a progressing emotional disorder. Only when the chemical data were assembled did we find that some of the changes had not returned to normal till Period VI with a normal diet.

Procedures

The formula, vitamin and mineral supplements are indicated in Table I. The pattern is similar to that reported previously.[1-4] The calorie intake in

TABLE I

Composition of Formula		Vitamin Supplement	mg	Composition of Salt Mixture	mg
Granulated sugar	200 gm	Thiamine hydrochloride	1.2	Calcium biphosphate	67.9
Cornstarch	5 gm	Riboflavin	1.8	Calcium lactate	163.5
Water	50 ml	Pyridoxine	2.0	Ferric citrate	14.9
Vitamin free casein	125 gm	Ascorbic acid	50.0	Magnesium sulfate	68.5
Corn oil	[illegible]0 gm	Niacin	12.0	Dibasic potassium phosphate	119.9
Cystine	[illegible]0 mg			Sodium biphosphate	43.6
Vitamin A	5330 U S P units			Sodium chloride	21.8
Vitamin D	1070 U S P units				
$NaHCO_3$	10 gm				
Calories	3000				

Contains 20 mcg Vitamin B_{12} by assay.

Coffee and soft drinks allowed ad libitum but measured brought the average intake of potassium to 1.2 grams a day.

We were enabled to do the study with prisoners as volunteers through the thoughtful cooperation of Mr. Roy Purcell, warden of the Iowa State Reformatory at Anamosa, and with the authorization of the State Board of Control, Mr. Henry W. Burma, Chairman.

After a period of two years of investigation using pantoyl taurine which proved to be inert we began a series of observations using omega methyl pantothenic acid and a purified ration devoid of pantothenic acid

In previous investigations of pantothenic acid metabolism in human subjects Bean Hodges Daum and Thornton[1 2 3] described metabolic abnormalities and clinical signs which occurred in normal young men given the pantothenic acid antagonist omega methylpantothenic and a diet devoid of pantothenic acid The signs were those of an illness characterized by torpor, apathy and depression cardiovascular instability especially in the erect position a neuromotor disorder with paresthesias burning sensations and muscle weakness abdominal pains and disturbance of alimentary function and frequent infections Biochemical alterations included an inconstant reduction in the percentage of PABA excreted in the urine in the acetylated form irregularities in glucose tolerance and increased sensitivity to insulin a failure of ACTH to induce eosinopenia an irregular reduction in 17 ketosteroid excretion and the development of a histamine refractory achlorhydria without any disturbance in gastric motility The illness induced in the subjects caused us to abandon the planned recovery period and employ cortisone a rich diet and added vitamins Because the abnormalities had not been anticipated because of the hazard and the inherent difficulties in such studies in human subjects the experimental design was not without limitations very obvious in retrospect For these reasons it was desirable to repeat and extend the observations

Experimental Design

We planned the present study with more elaborate control periods (Figure 1) Period I was designed to establish baselines and the test routines while

PATTERN OF
TEST PERIODS DIETS VITAMINS & ANTAGONISTS

TEST PERIODS	I	II	III	IV	V	VI
DURATION days	14	14	14	35	7	12 LK 23 WS
DIET	GENERAL oral	SPECIAL tube				GENERAL oral
VITAMINS Pantothenic Acid (mg/day) Others as in Table I	30	430			490	430
ANTAGONIST Omega methyl Pantothenic Acid (mg/day)				500		

* TEST RAN LK 1 24 55 to 4 30 55
WS 1 24 55 to 5 11 55

no muscle tenderness He felt that his over all strength was improving A week later he had less muscular cramping The paresthesias persisted He was much more lethargic and somnolent He spent most of the time in bed It was only with difficulty that he could be aroused in the morning After four weeks of Period IV for the first time a positive Trousseau sign was demonstrated and the tendon reflexes became still more inactive Two days before the end of Period IV he had repeated bouts of nausea increasing somnolence and moderately severe muscle cramping and paresthesias One day after the start of Period V nausea became troublesome It was only with difficulty that he could retain the tube feeding Only 24 hours after Period VI was begun there was complete cessation of the paresthesias in subject W S and he became less somnolent A week later the muscular cramping was gone and the Trousseau sign was negative He felt wonderfully well All lethargy somnolence and weakness were gone Diminution of tendon reflexes remained

I H remained asymptomatic until 11 days after the start of Period IV when she had muscle pains in the legs calf muscle tenderness and slight unsteadiness of gait No definite reflex changes were demonstrable Seventeen days after beginning Period IV she had intermittent spontaneous carpopedal spasm in addition to severe menstrual cramps without bleeding Thigh and calf muscles were extremely tender Paresthesias had developed in the lower extremities The remainder of the neurological examination was negative After 22 days of Period IV she noted some lessening of the muscle cramps but the paresthesias persisted along with a definite increase in lethargy and somnolence During the last week of Period IV she was nauseated and refused her tube feeding on 4 occasions After four days of Period V her clinical status was unchanged except that some disorientation and hallucination occurred She kept saying People are taking pictures of me During the last few days of Period V she became extremely depressed cried frequently and often repeated I want to kill myself After five days of Period VI she was completely asymptomatic She felt better than she had for many months No abnormalities of the tendon reflexes could be demonstrated

No significant lability of pulse rate or change in blood pressure or pulse pressure occurred in any subject Electrocardiograms failed to reveal any abnormalities in subject H T until the beginning of Period IV when the U waves in the precordial leads became prominent In W S repeated electrocardiograms were normal until the beginning of the second week of Period IV at which time T wave and U wave changes in the precordial leads were those seen in hypokalemia (Figure 2) In I H control electrocardiograms revealed a prolonged QTC interval and abnormal T waves As the experiment progressed she also developed additional abnormalities

Periods I and VI was the same as during the time the formula was used W S was the only normal subject on whom we collected complete data In another young man the experiment was stopped after two weeks of Period IV because of a breach of control The other subject, a 31 year old white woman had obesity and the adrenogenital syndrome We wanted to see whether the antagonist and deficient diet might reduce her adrenal cortical overactivity We used a 1000 calorie reducing diet throughout the whole study She got only a third of the quantity of formula but the same supplement of vitamins and minerals

In our present studies we concentrated on fluid and electrolyte problems while repeating many of the studies we had done previously

The original plan was somewhat different for the patient L H Her control period on a general diet lasted 8 weeks from January 12 1955 to March 7 1955 On March 7 she started the pantothenic acid deficient tube formula and 500 mg of omega methyl pantothenic acid She then had a 5 week period exactly like that of Period IV of W S Period V likewise was identical with that of subject W S as was Period VI with the exception that in the case of L H it lasted only 12 days for W S it was for 23 days

Results Clinical

H T had no symptoms until the beginning of the second week of Period III Then he first noted increasing fatigue slight weakness and transient unsteadiness upon standing upright These symptoms although nonprogressive were unrelenting No personality change was noted He remained pleasant and cooperative Four days after the start of Period IV he first had flexor spasms of the right forearm and hand Three days later, paresthesias of the upper and lower extremities began Repeated neurological examination failed to reveal any abnormalities until 8 days after the start of Period IV when a slight but definite decrease occurred in the tendon reflexes on the right side This progressed for three days and then remained stationary No other symptoms or abnormal signs appeared Subject W S was asymptomatic until the beginning of the second week of Period III Then he noticed the onset of increasing fatigability a generally tired out feeling mild weakness and unsteadiness of gait on arising in the morning Three days after the beginning of Period IV he had cramps of the right anterior thigh muscles and severe pain in the right Achilles tendon At the end of the first week of Period IV paresthesias of the upper and lower extremities began By the next day he was extremely torpid and for the first time the tendon reflexes on both sides had decreased Otherwise the neurological examination and physical examination were normal Two weeks after the start of Period IV W S was troubled by severe muscular spasms of his hands forearms and legs Although the paresthesias persisted there was

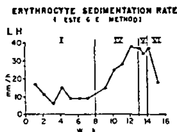


Fig. 3 The increase in sedimentation rate

urinalysis. Weekly eosinophil counts failed to reveal any significant variation.

Results Metabolic

Eosinopenic response to ACTH

In one subject H T no significant alteration was noted. In both L H and W S there was a definite decrease in the eosinopenic response to ACTH beginning in Period IV and continuing through Period V and VI (Figure 4).

Kepler Power Robinson Test

Subject H T had one abnormal test during Period II but all other tests were normal. Subject W S had an abnormal test during Period I and II

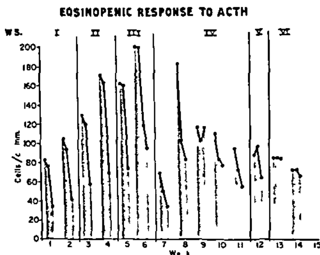


Fig. 4 The eosinopenic response to ACTH

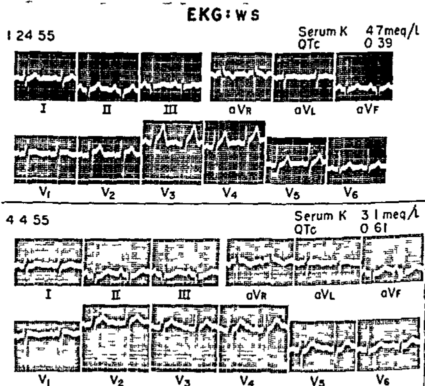


Fig The electrocardiogram b fore and during hypok ilemia

Ballistocardiograms of H T were normal until the first week of Period IV when definite abnormalities appeared In patient L H control ballisto cardiograms of *H T were normal until the first week of Period IV when* definite abnormalities appeared In patient L H control ballistocardio grams revealed bizarre complexes In W S no abnormalities developed Chest films failed to reveal any alterations Gastrointestinal changes were similar to those reported previously [3] During Period IV none of the sub jects had upper respiratory infections or other manifestations of decreased bacterial resistance W S and L H had a progressive increase in the sedi mentation rate after the beginning of Period IV (Figure 3) It promptly re turned to normal early in Period VI No alteration in the sedimentation rate of subject H T occurred during the control period but it increased after one week of Period IV During the experiment there was no signifi cant change in the weight of subjects W S and H I L H lost weight on the 1000 calorie diet at the same rate in all periods No significant altera tions were noted *in the hemoglobin red blood count white blood* count or

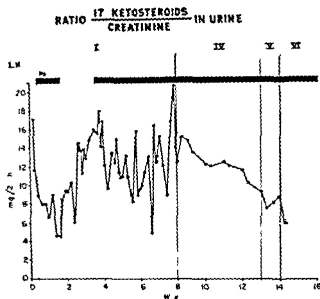
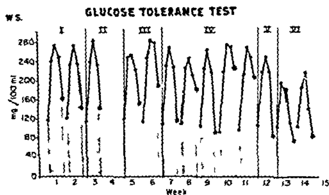


Fig Acet lation f PABA

urine paraminobenzoic acid wa again tarted This was followed by a light but definite decrease in the amount of excreted 17 ketosteroids Ex cretion of 17 ketosteroid however was till above normal A definite decrease in urinary excretion of 17 ketosteroid from this level was noted in Period IV and V as well as Period VI in this subject



Fi Glu se tol ra te t

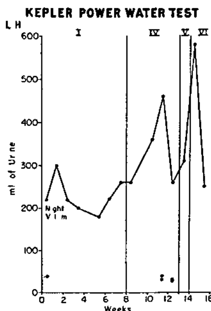


FIG 5 Water excretion test

but subsequently it became and remained normal A striking aberration occurred in L H Numerous tests during the control period were all well within normal limits During Period IV she developed an extremely abnormal response as manifested by an inability to excrete the water load The test remained abnormal until after the start of Period VI (See Figure 5)

Para aminobenzoic Acid Acetylation

Acetylation of a standard dose of PABA did not change significantly in any subject throughout the study

17 Ketosteroid Creatinine Ratio

In subject H T no significant change occurred In subject W S a definite decrease in the excretion of 17 ketosteroids occurred toward the end of the Period IV It persisted through Period V and the early part of Period VI Before the study L W had a greatly increased 17 keto teroid excretion At the beginning of the control period para aminobenzoic acid was given to test acetylation As soon as PABA was given there was a prompt fall in the urinary excretion of 17 keto teroid (See Figure 6) It again became markedly elevated when para aminobenzoic acid administration was stopped While again excreting large amounts of 17 keto teroids in the

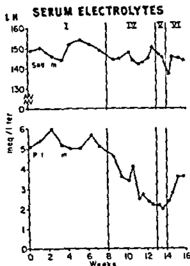


Fig. 10. Serum sodium and potassium.

began in Period III and persisted through Periods IV and V (See Figure 8). I. H. likewise had a great increase in insulin sensitivity.

Serial determinations of serum calcium and phosphorus failed to reveal any alteration (Figure 9). W. S. had a slight elevation of alkaline phosphatase during the latter half of Period IV, which persisted during V and VI. Serial blood urea nitrogen determinations revealed no alterations from the control values nor did repeated sodium determinations. Alterations in the serum potassium, serum chloride and CO_2 combining power were of striking magnitude. In subject H. T. a trend toward the development of hypochloremic alkalosis with hypokalemia began during the first week of Period IV. In subjects W. S. and I. H. extreme degrees of hypochloremic alkalosis and hypokalemia developed during Period III, IV, and V with a rapid return to normal during Period VI (Figures 10 and 11).

Serum Protein Studies

In all subjects the albumin and total proteins remained normal. There were definite alterations in the electrophoretic pattern with an increase in the alpha I and alpha II globulins during the deficient periods in all three subjects with a return towards control level during Period VI. In I. H. there was also a definite decrease in the beta globulin during Period IV. No significant alterations in total protein or albumin or globulin occurred (Figure 12).

Glucose Tolerance Test

In W S, marked alterations occurred Although he had an abnormality of his glucose tolerance test throughout the entire study during the latter part of Period III and throughout Period IV a new abnormality occurred (Figure 7) This was characterized by a persistent elevation in the 2 hour blood sugar determination This alteration was lost promptly during Period V and did not recur Likewise in I H a similar alteration occurred During Periods IV V and the early part of Period VI an elevation of the 2 hour blood sugar occurred The curve returned to the control form after the first week of Period VI

Insulin Tolerance Test

In subject H T an increase in sensitivity to insulin was noted during Period III and IV with the 20 minute blood sugar much lower than in the control tests In subject W S a marked increase in sensitivity to insulin

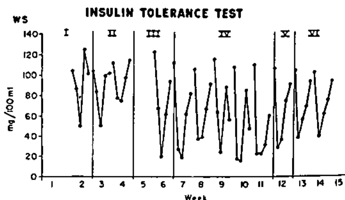


Fig 8 Insulin sensitivity test

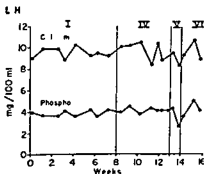


Fig 9 Calcium and phosphorus

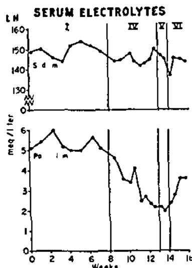


Fig 10 Serum sodium and potassium

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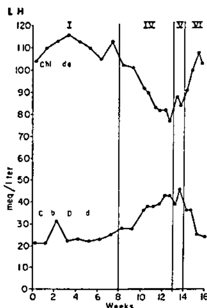


Fig. 11 Serum chlorides and carbon dioxide

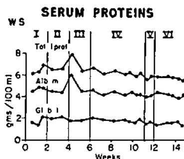


Fig. 12 Plasma globulin fraction

Liver Function Tests

Liver function studies including the bromsulphalein test thymol turbidity cephalin flocculation zinc sulfate turbidity and serum bilirubin determinations were performed every two weeks in subject W S No alterations were noted

Cholesterol and Cholesterol Esters

Figure 13 gives a representative curve for the changes in cholesterol and esters There was a sharp fall in both components while the tube feedings were used with a return to normal when the normal diet was restored Total serum fat and phospholipids showed no significant changes

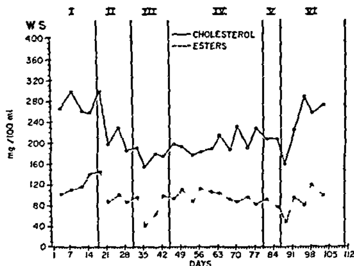


Fig 13 Cholesterol and esters

Prothrombin Activity

A ratio of the control prothrombin time to the patients prothrombin time times 10 was arbitrarily selected as a measure of prothrombin activity Using this ratio there was a definite decrease in prothrombin activity during the deficient period in subject W S with a rather prompt return to control levels during Period VI A similar but somewhat less marked decrease in prothrombin activity occurred in subject L H (Figure 14)

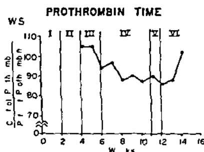


Fig 14 Prothrombin time

Discussion

In our previous studies we were impressed by the clinical illness which occurred when the deficient diet and omega methylpantothenic acid were used together. In the present study there was a similar weakness, fatigue and decrease in spontaneous activity. Mood changes, though they did develop, were not as impressive as those observed in previous tests. Dizziness and unsteadiness were severe. Sometimes changes in position were awkward because of the temporary instability. At least some of the fatigue, weakness and awkwardness seemed to be caused by the neuromuscular disorder. It is impossible to say whether mental disturbances were responsible for one of the subjects going A.W.O.L. but such behavior is hardly surprising under the circumstances of the test. One subject developed a psychosis with paranoid features which continued into Period V but rapidly vanished during Period VI. The torpor and somnolence began to diminish very soon after the antagonist was stopped and pantothenic acid was given in Period V, suggesting strongly that the induced state of pantothenic acid deficiency was responsible for such changes. The neuromuscular abnormalities consisting of paresthesias, weakness, cramps, tenderness and alteration in tendon reflexes, muscle tenderness and the positive Trousseau sign did not all clear up till Period VI but there was a very definite improvement in Period V when pantothenic acid was substituted for the antagonist.

The subjects in the present test did not exhibit much vascular instability, postural hypotension, labile pulse or easily provoked tachycardia which had all been so prominent in earlier studies. The ballistocardiograms became abnormal in one subject. Having been abnormal in the control period of another subject, they changed towards normal. Such observations do nothing to clarify the nature of the circulatory status of the subjects or the vagaries of the ballistocardiogram.

There was no tendency for the subjects to have infection though the conditions of the metabolic ward and of the entire experiment were unchanged from previous tests when infection prevailed during the period of deficiency. There was, however, a striking increase in sedimentation rate which returned to normal in Period VI. The reason for the increased speed of sedimentation is not known.

Several metabolic changes were studied in detail. In subject W. S. the eosinopenic response to ACTH did not decline until Period IV when the antagonist was given. By the third week of the deficient period the response had diminished conspicuously. In contrast to our previous observation, this did not come back to normal during the recovery period. The failure of restoration to normal when pantothenic acid was given and when the diet was normal may mean that the mechanism responsible was disturbed more seriously than in the earlier studies when the deficiency and antagonist period was 4 rather than [illegible] weeks in duration. Another possi

bility is that corti one which was used at the termination of the experimental period in the earlier test had some other effect on the adrenals The capacity of one subject to excrete a normal amount of urine in response to an ingestion of a large quantity of water was seriously impaired during the deficiency period but came back to normal during Period VI

The excretion of 17 ketosteroids is recorded in Figure 6 In one subject the initial levels were higher than normal and fell very promptly while PABA was given They then returned to the previous level when it was discontinued Subsequent administration was followed by a diminution of the ratio and then a tendency to level off at the previous control level During the period of induced deficiency there was a slow but rather steady decline which was still continuing at the time the last test was done during the recovery period The significance of the e findings is uncertain

The changes in glucose tolerance were characterized by prolonged elevation of the blood sugar which even after two hours tended to stay up around 200 or higher particularly during the latter part of Period IV This returned to normal during Period V and remained normal Study of the insulin tolerance test revealed that with the deficient diet alone a sharp increase of the insulin sensitivity occurred and this persisted throughout Period IV It was slowly being restored towards normal in Periods V and VI

Figure 10 shows the very significant fall in serum potassium and the relative stability of the level of serum sodium throughout the experiment These changes in serum potassium occurred during a period when the intake of potassium was constant Figure 11 shows the striking changes in blood chlorides and carbon dioxide Unfortunately we do not have data from balance studies so cannot say whether there was a potassium diuresis an absorption defect or whether potassium was stored in the body The electrocardiographic changes indicate that there was indeed a cellular depletion of potassium Since the absolute requirement of potassium is not known the possibility of an inadequate supply exists

Consistent but not very extensive declines in the prothrombin occurred during the deficient period but there was no sign of any liver malfunction nor was clinical bleeding at any time a problem

Speculation

This report deals with work in progress Slowly we are improving the experimental design which we hope eventually will enable us to understand the nature of the changes we have produced So far we cannot be sure that I) we have produced a defect in pantothenic acid metabolism by employing a metabolic antagonist which interferes with the diverse functions of coenzyme A II) whether omega methylpantothenic acid is a more powerful toxic agent working as a general protoplasmic poison or III) whether some unrecognized deficiency exists in the experimental diet

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As far as I is concerned many of the changes induced are similar to those induced in animals by pantothenic acid deficiency. Perhaps too much emphasis should not be put on the fact that glucose tolerance returned to control levels in Period V without change in diet but when pantothenic acid replaced the antagonist (see Figure 7). Many other abnormalities did not disappear until Period VI. In retrospect Period V was too short. We must emphasize the well known fact that correcting a specific deficiency in diet does not necessarily correct a lesion induced by the deficiency. Too little, too brief or too late may explain failures in correcting what has been called the humpty-dumpty situation.[4] Final proof will depend on our ability to titrate the human deficiency syndrome, if such it is, to the stage where it is still quickly reversible by merely replacing antagonist with vitamin. The interpretation of any vitamin antagonist's action must be made with knowledge that many subtle metabolic bypasses may enable the cellular and humoral economy to make remarkable adjustments.

Not knowing, except by inference and extrapolation, what coenzyme A and pantothenic acid do in human metabolism, interpretation of our data at the present merely tentative stage of work in progress is impossible. If one is willing to compare our observations with a miscellany of observations in a variety of animals and some of man, it may be that potassium deficiency alone is adequate to explain many of the clinical and biochemical changes.[6,7] Our next tests will inquire into that possibility. We propose to study the effects of large doses of potassium at a time when it is low. Likewise, administration of Coenzyme A may tell us whether that substance can correct the metabolic errors. The possibility that our metabolic machine is related to stimulation of aldosterone production and reduced production cortisone like compounds is a stimulating speculation.

If we have an unrecognized deficiency, a longer Period V should provide the clue.

Conclusions

Work on a syndrome induced in normal subjects and one with evidence of adrenal cortical overactivity confirms and extends our observations. A clinical state of lethargy, weakness, burning paresthesias and cramps with signs of tetany was observed. Low serum potassium might account for many of the clinical findings. Likewise, hypokalemia, hypochloremia, hypochlorhydria, metabolic alkalosis and a defect in carbohydrate metabolism were observed. Further studies are in progress to elucidate the mechanisms whose disordered function leads to these disorders.

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DISCUSSION

DR. HENRY ST. GEORGE TUCKER, JR. (Richmond): I was not entirely certain about one point. Were these evidences of adrenal insufficiency produced equally by the diet and by the pantothenic acid antagonist? Of course, the obvious question is: If they were produced by the antagonist, have you [illegible] given it to a patient with overactive adrenals, a patient with Cushing's syndrome?

DR. JOSEPH L. LILIENTHAL, JR. (Baltimore): I want to ask Dr. Bean, if I may, whether—in view of the changes in the serum carbon dioxide and potassium which suggest the alkalosis which occurs in potassium depletion—you had a chance to secure the evidence of loss in potassium in the urine during the period, or by any chance muscle biopsy, to see whether the affected muscles [illegible].

DR. IRVING S. WRIGHT (New York): In maintaining Dr. Bean went to [illegible] measures to produce this deficiency, I wonder if he has encountered any indications which he would regard as for the use of pantothenic acid therapeutically.

DR. JULIAN M. RUFFIN (Durham): I would like to ask Dr. Bean if the picture which he has just described ever occurs spontaneously in man in this part of the world. In other words, is a pantothenic acid deficiency of clinical importance?

DR. WILLIAM B. BEAN (Closing): I did not have time to go into a lot of things. Others are not quite as clear.

We have tried giving the antagonist in large doses to people on a normal diet, so far, over a period up to five weeks; we have not been able to produce a single one of the changes we have demonstrated in subjects on a deficient diet. We have not gone longer than six weeks on a deficient diet without the antagonist, [illegible] we have not [illegible] the full [illegible] progress. How many weeks would be able to tell whether a [illegible] can be induced by [illegible] diet alone.

We have tried giving omega methyl pantothenic acid to patients with advanced or terminal carcinoma in the hope that we might be able to induce a medical adrenalectomy; adrenal [illegible] and we have given it to one person with a [illegible]

genital syndrome. In cancer we induced no clinical improvement nor did we have laboratory evidence that we had done anything important metabolically.

As for Dr. Lilienthal's question, when we began to pick up the spilled and broken pieces and analyzed the data when the experiment was over we realized we had left undone those things we ought to have done and had done those things which we ought not to have done, and we were sort of worried about it. We are now doing a balance study. This all happened on a relatively fixed and we hope normal intake of potassium and other electrolytes. We have studies going now on the urine and feces as well as what comes in. You might explain those data by saying (1) potassium was not absorbed, (2) that it was lost in excessive amounts in the urine. We have no reason to suspect that they lost any extra amounts in the stool.

It is obvious to those who are studying the latest medical reports in LIFE, TIME and other medical journals which keep us up to date (laughter) that if I were an aldosterone man I might say that these subjects might have been manufacturing extra aldosterone—in other words, we may have been stimulating one part of the adrenal cortex and diminishing another. At least, one can explain these things on the basis that there is too much aldosterone, or that there is simply a wastage of potassium from somewhere in the system. But we have not studied either urine or muscles.

The implication is that pantothenic acid is useful, but our terrible difficulty in trying to find a deficiency in anything which resembled food should be emphasized. We measured anywhere from two to three, four or five times the actual pantothenic acid in the diet that the tables indicate is present in the food.

A warning, I think, should be voiced here. The work of Becker and Friedenwald in alloxan induced diabetes in rats has demonstrated that those animals, when given a pantothenic acid deficient diet, are spared some of the unhappy consequences of alloxan diabetes. When given pantothenic acid, the vascular changes occur either accelerated in time or worse in degree, suggesting that an imbalance may stir up the adrenal cortex under those peculiar circumstances.

Thus, because pantothenic acid is present in a liberal quantity in any conceivable diet—it is probably a waste of money to put in more pantothenic acid. We do not know enough about it. I trust that the vitamin magnates and manufacturers do not seize upon our data as reason to needle their already curiously needled vitamin packets with even more vitamins.

As far as Dr. Ruffin's comment is concerned, there has been in nutritional literature—I should say malnutritional literature, if I may call it that (laughter)—over the last hundred years a description of burning feet. Our subjects developed paresthesias which were precisely similar, as far as you can judge somebody else's burning feet, to what had been described in medical literature.

A man by the name of Gopalan in 1946 described the burning foot syndrome among Indians in India. These people were literally starving and ate a most peculiar diet. The Indian diet, as you know, varies in all kinds of different directions. He gave them nicotinic acid, thiamine—I do not think he had any B 6 at the time—riboflavin singly and in combination. There were dozens of subjects, so he had a good experimental group. Nothing happened to the burning feet. Then he gave *calcium pantothenic* and the burning feet no longer burned. I suspect that there may have been a spontaneous pantothenic acid deficiency in these people.

The evidence, however, looked at from this distance, is merely a clinical inference. We have tried it on many people with various neuropathies and have not seen that it has done any good.

JOINT AND BONE DISEASE DUE TO MYCOTIC INFECTION

By ELAM C TOONE Jr M D and (by invitation) JOHN KELLY M D

RICHMOND

The importance of pathogenic fungi as a cause of bone and joint disease has taken on added significance as the result of several developments. First, the control of pathogenic bacteria with chemotherapeutic and antibiotic agents has increased the relative frequency. Second, increased travel incident to military service and other factors has resulted in a dissemination of fungus infections. Third, therapeutic agents of a more effective nature for several of the mycotic organisms have become available recently.

Twenty five cases of fungus disease observed at the McGuire Veterans Hospital and the Hospital Division of the Medical College of Virginia in a five year period from 1949 through 1954 have been reviewed. This included 11 cases of blastomycosis, 4 of coccidioidomycosis, 4 of cryptococcosis, 3 of actinomycosis, 2 of histoplasmosis and 1 of nocardiosis. In eight cases there was involvement of bone or joint (Table 1).

The incidence of mycotic infection is much larger than is generally appreciated.[1-10] The types of infection encountered here are about as anticipated for this area with the possible exception of the four cases of coccidioidomycosis. Each of these, however, gave a history of having traveled or maintained a residence in one of the endemic areas of California. The age range varied between 18 and 54 years and was not felt to be unusual. There was only one female patient in the group of 25 cases. This correlates with the general predominance of systemic fungus infections in males, but the series could not be considered representative since 18 of the 25 cases were observed at the McGuire Veterans Hospital, which has an almost negligible number of female patients. Fourteen patients were white and 11 Negro, and there was no evidence of racial susceptibility except in the four cases due to coccidioidomycosis infection. Three out of these four cases were among Negroes, and in two of these the disease was disseminated and progressive. The deeply pigmented races have been found to be more susceptible to this infection, and the disease is usually more serious.[1]

There has been a popular, although probably incorrect, conception that systemic fungus disease is restricted to rural areas and to individuals in the lower income groups. In this series 14 patients were from rural areas—eight farmers, five laborers and one Pullman porter. Eleven patients were

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TABLE 1

Fungus Disease	Total Number of Cases	Number of Cases with Bone Involvement
Actinomycosis	3	0
Blastomycosis	11	5
Coccidioidomycosis	4	1
Cryptococcosis	4	2
Histoplasmosis	2	0
Nocardiosis	1	0
Total	25	8

from urban centers—three laborers two executives one teacher one policeman one clerk one student one textile worker and one who at the moment was unemployed but who had been discharged recently from the United States Marine Corps (Table 2)

Of the total number of 25 cases reviewed three types of mycotic organisms produced joint and bone lesions These were Blastomyces Dermatitidis Cryptococcus Neoformans and Coccidioides Immitis A brief review of the disease pattern produced by these organisms will be made and representative case histories presented (Table 3)

Blastomycosis[1 3 10]

North American blastomycosis is probably limited to the United States and Canada The causative organism is the Blastomyces Dermatitidis which is a single budding yeast like cell with a thick refractile wall The source of this organism and its mode of invasion are unknown The infection may take either of two clinical forms Cutaneous or systemic In the systemic form the skin lungs and bone are chiefly involved with the latter occurring probably in over half of the cases Any of the bones of the body may be affected but the cancellous more often than the tubular The process is usually an osteolytic one with little or no surrounding bone reaction or production Recent reports have shown that stilbamidine and 2 hydroxystilbamidine have been effective therapeutic agents

Case Report J D A 50 year old Negro male was admitted to St Philip Hospital of the Medical College of Virginia on September 14 1954 The general health had been good until six weeks prior to admission at which time multiple furuncles in the region of the right wrist right great toe and the dorsum of the left foot developed One week prior to admission pain swelling and redness developed in the right knee both ankles and the right wrist For two weeks there had been slight anorexia malaise and a low grade fever *Physical examination* Draining sinuses of the right

TABLE I

Patient	Age	Sex	Race	Occupation	Residence	Diagnosis	Bone Involvement	Involvement Other Than Bones
S I	30	M	W	Farmer	Rural	Actinomycosis	0	Cervical node
M R	41	M	W	Farmer	Rural	Actinomycosis	0	Cervical node
J R	3	M	W	Lumber mill worker	City	Actinomycosis	0	Cervical node
W D	[illegible]	M	W	Laborer	Rural	Blastomycosis	0	Lungs and skin
M G	4	M	W	Executive	City	Blastomycosis	0	Lung
K U	40	M	C	Laborer	Rural	Blastomycosis	+	Lung
J D	5	M	C	Laborer	Rural	Blastomycosis	+	Disseminated
C T	[illegible]	M	W	Farmer	Rural	Blastomycosis	+	Disseminated
A H	[illegible]	M	C	Farmer	Rural	Blastomycosis	0	Disseminated
R M	51	M	W	Lumberman	Rural	Blastomycosis	0	Skin
E T	3	M	C	Farmer	Rural	Blastomycosis	0	Disseminated
I B	43	M	W	Policeman	City	Blastomycosis	+	Disseminated
P T	3	M	C	Farmer	Rural	Blastomycosis	0	Disseminated
J T	23	M	W	Textile worker	City	Blastomycosis	+	Lung
U H	3	M	C	Pullman porter	Rural	Coccidioidomycosis	0	Disseminated
M D	43	M	C	Farmer	Rural	Coccidioidomycosis	+	Lungs
W J	[illegible]	M	C	Carpenter	Rural	Coccidioidomycosis	0	Lung
J W	24	M	W	Store clerk	City	Coccidioidomycosis	0	Lung
J H	35	M	W	Executive	City	Cryptococcosis	0	Lung
R J	18	F	C	Student	City	Cryptococcosis	+	Disseminated
A I	41	M	C	Laborer	City	Cryptococcosis	0	Meninges
B G		M	C	Farmer	Rural	Cryptococcosis	+	Disseminated
H S	31	M	W	Laborer	City	Histoplasmosis	0	Lung
A C	46	M	W	[illegible]	City	Histoplasmosis	0	Lung and skin
J B	24	M	W	[illegible]	City	Nocardiosis	0	Disseminated

wrist right great toe and dorsum of the left foot were present There was painful swelling and redness of both ankles the right knee and right wrist Both the liver and spleen were barely felt on deep inspiration Inspiratory and expiratory crepitant rales were heard in both lung bases *Laboratory data* A direct smear from the sinus of the right wrist area was positive for Blastomyces Dermatitidis The hemoglobin was 7 8 gm erythrocytes

TABLE 3

Patient	Diagnosis	Extent of Bone Involvement
K. U.	Blastomycosis	Right patella and tibia
J. D.	Blastomycosis	Right ulna, proximal phalanx of right great toe, right sacro-iliac joint and 3rd and 4th lumbar vertebrae
C. T.	Blastomycosis	Cuneiform, scaphoid, cuboid, and the 1st, 2nd and 3rd metatarsals of the left foot
I. B.	Blastomycosis	Sacrum
J. T.	Blastomycosis	Talus, calcaneous, tarsals and the 2nd and 3rd cuneiform of right foot
M. D.	Coccidioidomycosis	Cervical and dorsal vertebrae
R. J.	Cryptococcosis	Rib, sternum and pelvis
B. G.	Cryptococcosis	Skull, pelvis, right acromial process, right humerus, right tibia and the right 1st metacarpal

2,620,000, leukocytes 17,400, polymorphoneutrophils 97%. A urinalysis showed an albumin of 1 plus and many white cells in the sediment. Six blood cultures were negative and three sputa specimens showed no tubercle bacilli. X-ray examinations: There was extensive bone destruction of the distal third of the right ulna with a pathologic fracture present, moderate destruction of the proximal phalanx of the right great toe, a few punched out areas in the region of the right sacroiliac joint, a mottled "moth-eaten" appearance of the bodies of L-3 and L-4 vertebrae with necrosis and fracture of the transverse process of L-4 and moderate destruction of the right patella. A chest film showed mottled infiltration throughout the right lung field and the mid zone of the left. There was a small amount of fluid in the right costophrenic angle. Course in hospital: The patient was considered acutely ill at the time of admission and died four days after entering the hospital. A single 100 mg. dose of 2-hydroxystilbamidine was given intravenously on the day prior to death without any noticeable clinical effect (Fig. 1).

Cryptococcosis[4, 5, 6]

Cryptococcosis is world wide in distribution. The infection is caused by the Cryptococcus Neoformans, a single budding yeast-like cell with a thick capsule which can be clearly demonstrated by an India ink preparation. The organism has a known saprophytic existence in nature, but the mode of invasion in man is not understood. The disease has a marked predilection for the central nervous system, but the skin, lungs and other organs may also be affected. Joint and bone involvement is said to be rare but does occur. The process is almost purely an osteolytic one with little or no reaction occurring in the surrounding bone or periosteum, and no



FIG 1 Case No 1 Osteolytic change distal one third of right radius and ulna with pathologic fracture of right ulna Blastomycosis

tendency to bone production There seems to be an affinity for various bony prominences otherwise almost any bone in the body may be affected Encouraging results in treatment with stilbamidine and 2 hydroxy stilbamidine have been reported recently although the organism does not appear to be influenced as strongly by these drugs as does the Blastomyces Dermatitidis The central nervous system involvement is particularly resistant to treatment

Case report B C A 27 year old Negro male was admitted to St Philip Hospital of the Medical College of Virginia on January 20 1952 There had been a cough productive of clear sputum for five months and pain swelling and limitation of motion of the right shoulder for two There was an additional history of weight loss malaise and temperature elevation At the age of five years osteomyelitis of the right leg had developed follow

ing traum i and the use of a leg brace since that time had been necessary *Physical examination* The temperature was 103 2 degrees Fahrenheit the skin was hot and dry and the patient was described as being lethargic A tender fluctuant 8 × 3 cm mass was present over the right acromial process There was a moderate generalized discrete lymphadenopathy, and the spleen was barely palpable *Laboratory data* The Cryptococcus Neoformans was found on smear and culture in material aspirated from a mass over the acromium and on culture of the urine The urine otherwise was negative except for a slight amount of albumin There was a persistent eosinophilia of 10% but the hemogram otherwise was not remarkable Spinal fluid examination was entirely normal X ray examinations Sharply defined punched out areas were present in the skull proximal end of the first left metacarpal the right acromial process the shaft of the right humerus and in several ribs There was al o extensive widening and thickening of the right tibia indicative of marked bone productive changes and probably resulting from the old osteomyelitis presumably bacterial Chest x ray showed a moderate hilar adenopathy and a moderate degree of diffuse fibrosis Hospital course Initial treatment consisted of the use of symptomatic and supportive measures with no appreciable change in the



Fig 2 Case No 2 Osteolytic change of the skull Cryptococcosis

clinical status and the patient left the hospital against medical advice after one week. He returned six weeks later after having developed fluctuant masses over the forearm and sternum. Cryptococcus Neoformans were cultured from these areas as well as from the sputa and the urine continued positive. Treatment with 2 hydroxystilbamidine intravenously was then instituted for 20 days in a daily dose of 225 mg. Following a rest period of 10 days this same course of treatment was repeated. Clinical improvement was prompt and quite marked with a return of temperature to normal, weight gain, disappearance of malaise and disappearance of the fluctuant masses in the various areas mentioned. A two months follow up x ray study of the bones however showed no change. This is a characteristic experience. The patient was last seen six months following therapy and appeared to be doing well clinically but efforts to have him return to the hospital for more detailed studies have not been successful. His present status is not known although casual information obtained from friends and members of the family indicates that his condition is quite satisfactory (Fig 2).

Coccidioidomycosis [7, 8, 15]

Coccidioidomycosis is endemic in the southwestern part of the United States and is particularly prevalent in the San Joaquin Valley region of California. The causative agent is the Coccidioides Immitis which is a round thick walled organism containing numerous endospores. It is found in the soil and it is believed that invasion occurs by inhalation. The disease takes one of two forms. The benign pulmonary infection or the chronic progressive and often fatal systemic. In the latter the skin, bones and other organs may be involved by spread from the original pulmonary infection which usually is progressive. Bone lesions are quite common and usually appear as cyst like areas of osteolysis. Proliferative periostitis may be present although frequently there is no surrounding bone reaction. To date no effective therapy has been reported for the progressive systemic type of coccidioidomycosis.

Case report M D. A 42 year old Negro male farmer while serving with the Army at Mather Field California in 1946 had been found to have an infiltration of the left lung field which was presumed to be tuberculosis although no organism was identified. For the next year symptomatic treatment was instituted with improvement of the pulmonary infiltration but with the appearance of a destructive process involving several of the dorsal vertebrae. Shortly after discharge from the Army in 1947 he entered a Veterans Administration hospital. No definite diagnosis was established but a year's therapy with streptomycin and para amino salicylic acid was given. Nine months following this course of treatment a fluctuant

mass in the upper dorsal region became evident In 1950 he was admitted to McGuire Veterans Hospital, in Richmond, Virginia because of this and the mass was incised and drained Smear and culture of the purulent material obtained were positive for Coccidioides Immitis Symptomatic and supportive treatment was continued principally at home and the process apparently became stable In 1951, he was recalled to McGuire Veterans Hospital for further evaluation There were two small draining sinuses present in the upper right dorsal region of the back, and complete fixation of the cervical spine Laboratory studies Smear and culture made from material removed from the draining sinuses were positive for Coccidioides Immitis The hemoglobin was 8 9 gm erythrocytes 3 090 000 leukocytes 15 000 with a normal differential count The urine showed a 3 plus albuminuria and was otherwise negative X ray examinations The chest x ray was reported as being negative and showed no evidence of any residual infiltration The cervical and dorsal spine showed productive bone changes with bridging between the last four cervical vertebrae There was evidence



FIG 3 Case No 3 Irregular destructive change along the anterior margin of D, with bone productive change of the body of this vertebra Coccidioidomycosis

of bone destructive and productive changes in the seventh, eighth and ninth dorsal vertebrae. *Shortly thereafter the patient left the hospital* against medical advice. In November 1953 the patient was admitted to another Veterans Administration hospital and expired the following day. Postmortem examination showed a large paravertebral abscess in the right upper dorsal area with bone destructive and productive changes in the lower cervical and upper dorsal vertebrae. Coccidioides Immitis was identified in the material obtained (Fig. 3).

Comment

Pathogenic fungi must be considered in the differential diagnosis of all infections involving bones and joints. Although neither clinical studies nor x-ray examination can make an absolute distinction between a mycotic and a bacterial infection, there are certain distinguishing features that will aid in the differentiation. Mycotic joint and bone disease occurs as a part of a systemic infection. Dissemination or spread is by means of the blood stream with the possible exception of actinomycosis in which case direct extension occurs. The lesions are usually multiple, wide spread, and in general show a predilection for cancellous rather than tubular bone. In the case of cryptococcosis there is a tendency towards involvement of the bony prominences.[1,2] The x-ray appearance is that of an almost pure osteolytic process with little bone or periosteal reaction except, again, in occasional cases of actinomycosis. Sequestrae, if present, are usually small, a contrast with the usual reaction resulting from bacterial infection. When joints are involved, it is usually by direct extension from the initial bone lesion, and extensive damage occurs to the bone, cartilage and synovial membrane. Roentgen evidence of bone damage may exist for many months after skeletal pain and signs of systemic infection have disappeared. Tuberculous bone and joint lesions are most apt to be confused with mycotic infections, and it may be almost impossible to differentiate the two. Solely from a roentgen standpoint, mycotic infection of the bone may be difficult to distinguish from multiple myeloma, certain cases of metastatic carcinoma, eosinophilic granuloma and other conditions. The clinical features of these varying diseases, however, should not offer real difficulty.[2,3,4,5,6,7,8]

The failure to respond to the usual antibiotic and chemotherapeutic agents should arouse suspicion that the infection is not one resulting from the usual pathogenic bacteria. The diagnosis, however, can only be made by recovering the organism from the joint, bone, abscess cavity, sinus tract, skin, sputum, urine or spinal fluid.

The prognosis for certain of this group of diseases has improved due to the introduction of the aromatic diamidines as more effective treatment

measures. Stilbamidine is unstable in solution and has been found to be toxic for the trigeminal nerve but 2-hydroxystilbamidine does not have these disadvantages and is equally effective. Blastomycosis, cryptococcosis (except of the central nervous system) and actinomycosis have proven to be the most effectively treated. The various sulfonamides and antibiotics have been effective in some cases of actinomycosis and nocardiosis. Iodides in various forms and quantities have formerly been the drugs used most extensively and for the longest period of time. This drug had been effective to a limited degree in the treatment of blastomycosis, cryptococcosis, actinomycosis and nocardiosis. Otherwise, the management has been largely symptomatic, supportive or with the use of a wide variety of drug and other treatment measures that enjoyed brief and unwarranted period of popularity. To date, no treatment of value is available for coccidioidomycosis, histoplasmosis or central nervous system cryptococcosis.[9, 15]

Summary

1. Eight cases of bone and joint disease were found in 25 cases of pathogenic mycotic infection observed in a period of five years. Five cases were due to the Blastomyces Dermatitidis, two to the Cryptococcus Neoformans, and one to the Coccidioides Immitis. The number and character of the mycotic infections were not considered unusual for this area.

2. Bone lesions, as a rule, are osteolytic in nature, usually multiple, and involve cancellous rather than tubular bone. Joint involvement occurs by extension from the adjacent infected bone. In cases responding to treatment, roentgen evidence of bone damage may exist long after the systemic features and evidence of involvement of other organs have disappeared.

3. The aromatic diamidines, particularly 2-hydroxystilbamidine, have been found to be effective in treating blastomycosis, actinomycosis and cryptococcosis (except of the central nervous system). Various sulfonamides and antibiotics have been helpful in some cases of actinomycosis and nocardiosis. Iodides in various forms are still being used in the treatment of a number of these diseases, but their use is limited. To date, no treatment of value is available for coccidioidomycosis, histoplasmosis or cryptococcosis of the central nervous system.

4. Diagnosis can be established only by recovering the organism from the joint, bone, abscess cavity, sinus tract, skin, sputum, urine or spinal fluid.

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DISCUSSION

DR ROGER O FOERBER (Los Angeles) I think Dr Toone's paper is very timely if our experience out west is any criterion We still see tuberculosis of the bone but certainly the other granulomatous diseases the fungi particularly seem to be popping up more and more frequently

I would like to bring out that in the treatment of at least coccidioidomycosis involving bone the treatment which existed for tuberculosis of the bone many years ago still holds true and we have people both Negro and white who purely on a supportive and rest regime have had improvement and apparent cure both from the complement fixation test and from the clinical picture by rest in bed by nourishing diet which has to be continued as with tuberculosis over a period of years

One of these cases had a badly involved ankle which did not look quite as bad as the foot Dr Toone has shown The other was a white man who had to have one leg amputated but the lesions which were many in the other leg gradually healed and he later died of other causes and had no evidence of coccidioidomycosis

DR THORNT SCOTT (Lexington) I should like to ask Dr Toone how many of

his patients with blastomycosis showed central nervous system involvement and if he found any therapeutic regimen to which those patients would respond

We have had five in the last two years in our community who responded systemically to stilbamidine but showed no response of the peculiar meningitis with which they were suffering

It is interesting to note that none of these patients was suspected of central nervous system involvement at the time they were referred to the hospital The course was very insidious and the meningitis presented none of the outstanding features of other forms of meningitis

At autopsy they showed healing of their systemic lesions in bone and lungs with stilbamidine but showed no response at all in the meninges

Dr David T Smith (Durham) This excellent paper of Dr Toone s and Dr Kelly s certainly emphasizes the increasing importance of the fungus infections both as diagnostic and therapeutic problems I was particularly impressed with his case of cryptococcosis (Torulosis) which recovered because I think this fungus has the highest over all mortality of all

There are many unsolved problems connected with cryptococcosis We have studied a number of the brain cases and they show neither skin sensitivity nor agglutinins to the organism One case which I studied had both pulmonary and bone lesions and did show a positive skin test to her own organism and also agglutinins which were easily demonstrable by ordinary test tube reaction Since this one did show agglutinins which were easily demonstrable that gives additional weight to the uniform absence of agglutinin in the meningeal case

The organism itself is vaguely reminiscent of the pneumococcus having a large diffuse polysaccharide capsule and also showing some evidence of response to sulfadiazine therapy In other words an occasional patient has recovered after sulfadiazine therapy

All this suggests purely theoretically the possibility that we have here an analogous situation to the pneumococcus polysaccharide which may flood the body and paralyze the immune mechanism as was first described by Dr Lloyd Felton If a large amount of the polysaccharide is injected into a mouse the mouse is unable to produce effective antibodies and will die from a very few organisms introduced furthermore he cannot be immunized by ordinary methods

All this adds up to the suggestion that in the case of cryptococcosis if the infection is limited and not too much of the capsule is produced ordinary immune bodies may result and the patients recover On the other hand if the body is overwhelmed with the polysaccharide you expect no immune response and the inevitable death of the patient

I believe it is worth trying 2 hydroxystilbamidine It is an inhibitor not a direct fungicidal agent the way it is for blastomycosis Dr Snapper reported four cases of coccidioidomycosis in the *Annal of Internal Medicine* a few months ago which suggests that 2 hydroxystilbamidine is helpful We recently had a very acute case contracted in the laboratory which was rapidly disseminating who made rather rapid recovery with this drug Of course that is just one case but the drug is harmless and since we do not know anything better it might be worth trying

Dr Worth B Daniels (Washington D C) We had a patient recently at our hospital who died with Hodgkin s Disease in cryptococcosis of the brain It might be interesting to call attention to the fact that the incidence of cryptococcosis is much higher in patients with *Hodgkin Disease than in other diseases* Infection with cryptococcus neoformans should be suspected when any patient with Hodgkin s Disease develops symptoms suggestive of central nervous system involvement

Dr. J. Whittington Gorham (New York): These large osteolytic lesions are of considerable interest. I would like to ask Dr. Toone if he had an opportunity to study either biopsy material or material at postmortem. I would be particularly interested to know whether osteoblasts were found or whether the tissue resembled the pannus formation which we see occasionally in cases of rheumatoid arthritis where there is marked absorption of bone.

Dr. Elam C. Toone (Closing): I believe Dr. Smith's remarks answered Dr. Ingberg's question regarding the treatment of coccyioidomycosis. Snapper has recently reported four cases treated with 2-hydroxystilbamidine with equivocal results. He summarized his article, however, by stating that he felt that the drug might have some controlling influence on the disease. Otherwise the only treatment has been that of rest and supportive measures.

Dr. Scott's remarks referable to the central nervous system involvement in blastomycosis are very interesting. We did have one case with central nervous system involvement and that patient died. It was the patient with the initial lesion in the sacrum, later developing an overwhelming disseminated infection. We have been aware, of course, that cryptococcosis is often associated with central nervous system involvement, but had felt that this was rare in blastomycosis.

In answer to Dr. Gorham's question: The bone and joint lesion here is not like that of rheumatoid arthritis. In mycotic infection the initial lesion is usually in the subchondral bone area with direct extension into the joint. The lesion is primarily a destructive one with osteolytic changes in the bone and little evidence of soft tissue resistance. In rheumatoid arthritis the initial lesion is in the synovial membrane with spread to the cartilage and subchondral bone. The tissue response in rheumatoid disease is characterized by an overproduction of granulation tissue.

I would like to thank the discussants for their questions and remarks, and have nothing to add to the points brought up by Dr. Smith.

PNEUMONITIS FOLLOWING ASPIRATION OF CRUDE OIL AND ITS TREATMENT BY STEROID HORMONES

By JOHN R. GRAHAM, M.D.

BOSTON

This is a report of a patient who aspirated large amounts of crude oil into his lungs and his treatment by steroid hormones. The patient was 39 years old. On August 9, 1954 he and a fellow worker approached a 13,000 gallon tank containing 8 inches of crude oil #5 at its bottom to clean it. The fellow worker entered the tank and was seen to fall unconscious into the oil. My patient went to his rescue, turned him on his back and then collapsed himself, falling on his right side with his mouth open and one nostril under the oil and one above the level of the oil. He remained there 15 minutes until rescued by firemen wearing special masks.

On the left of Chart I are listed the products which emanate from a petroleum fractionating column in the order of their volatility.[1] Thus at the top are the fuel gases, the alcohols, gasolines, kerosenes, heating or crude oils which are subdivided into 10 degrees of viscosity and of which the oil in our tank was #5—a thick, black, heavy oil. Then come the lubricating oils, waxes, residual oils and asphalt. The more volatile the product, the more acute and extensive is its damaging action on pulmonary tissue and the quicker is it removed from the body. Conversely, the less volatile products cause less acute reaction in the lung but remain in the lung for longer periods of time. The more volatile products are known to cause central nervous system depression and undoubtedly the fumes breathed by these men accounted for their coma. The oil aspirated by my patient is believed to have had some kerosene in it which is known to cause *severe pulmonary damage in a matter of minutes.* The large bulk of it was of a cruder mixture responsible for the prolonged irritant effect to the lung which will be observed in this case and which proved to be correspondingly slow in its evacuation from the body.

The patient was taken to the Boston City Hospital where he was revived from coma and shock after several hours and treated with oxygen and penicillin. He was extremely sick, had constant cough productive of blood tinged oil flecked sputum, was cyanotic and had a high fever. The X-rays here shown reveal the pneumonitis on the right (he had been lying on his right side) which was observed at that hospital.

Nine days later, on August 17, he was transferred to the Faulkner Hospital where his wife worked as a technician. On entry he appeared extremely ill, was wracked by a constant cough productive of oil and some

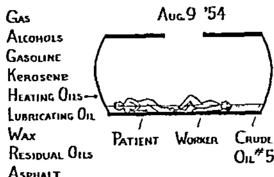


Chart I



blood was cyanotic dyspneic and had a temperature of 102 and pulse of 120

There were signs of consolidation in his right mid lung field rales all over the right lung and some on the left Urine and stools were normal white blood count was 32 000 Sputum showed a mixed flora of coliform alpha streptococcal and catarrhalis organisms Microscopic examination of the sputum showed blood polymorphs and black droplets of oil surrounded by histiocyte His vital capacity was 1 2 liters out of an expected 4 1 liters He had a penicillin rash and was consequently switched to achromycin streptomycin and later chloromycetin depending on sensitivity studies None of these antibiotics seemed to have any effect on his condition

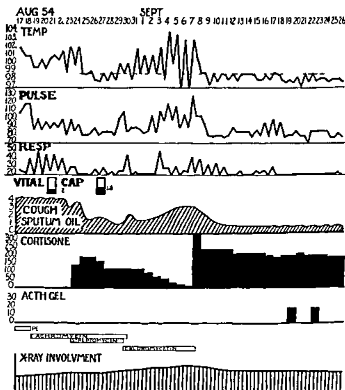


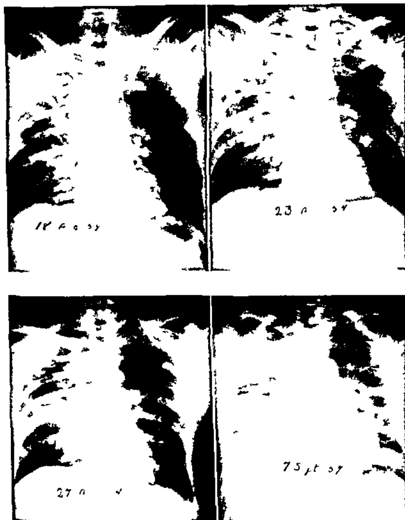
CHART II

A graphic representation of the clinical course of this patient is recorded in Charts II III and IV and representative X rays are herewith reproduced taken at significant points in his progress

Having originally felt that his pneumonitis might be in large part bacterial but having been disappointed in his response to antibiotics Dr Samuel Cohen who had been called in consultation and I decided to attempt to allay the chemical pneumonitis with cortisone Dr Albert Seeler and Dr Harriet Hardy specialists in industrial medicine although they had not met this particular problem before felt this was worth a trial

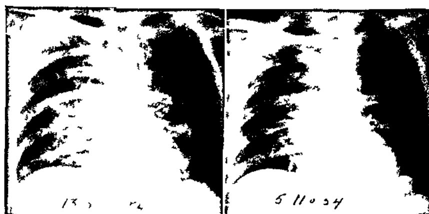
You will see by Chart II that the overt clinical manifestations of his illness were immediately benefited His temperature pulse and respiration became normal and his cough and sputum production decreased markedly

His X ray picture however did not show improvement and fearing that bacterial spread during cortisone therapy might be fatal we reduced and finally discontinued the cortisone As this was done the patient became clinically sicker and sicker The X ray dated September 7 shows the state of his lung as the cortisone was removed



At this point Dr *Maxwell Finland* was consulted and it was decided to reinstitute cortisone therapy and omit antibiotics keeping a sharp watch the while on his sputum and blood cultures You will note the immediate clinical response which was again obtained The concept then developed that we should give just enough steroid to keep the patient clinically well but still coughing so that he might eventually get rid of the oil

This policy was pursued with good effect ACTH was added twice a week to keep his adrenal cortex stimulated since we did not know how long



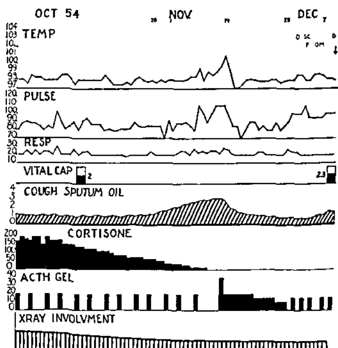
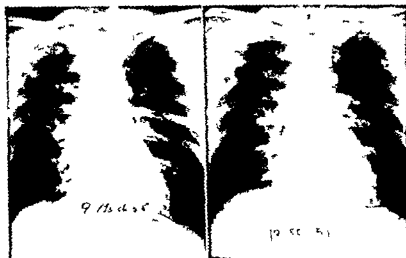


CHART III

cortisone therapy was to be continued. Over a period of six weeks cortisone was reduced gradually. Before it was eliminated a febrile episode and a return of chest signs, cough and more oil production recurred. These were quickly suppressed by more constant use of ACTH. The patient appeared so well that he was allowed to go home on December 10. His vital capacity was now 2.3 liters.



Over seven more months his ACTH was continued. A flare up of cough and sputum occasionally demanded a short increase in ACTH. Cough, *sputum and fever could be titrated against ACTH dosage in inverse proportion* throughout his course. In February 1955 he returned to activities on a part time basis. (He was studying to be a teacher at Boston University.) After examinations were over and vacation had begun, we gradually eliminated ACTH. He no longer brought up oil with his slight cough. Gradually his cough itself stopped. He has now been off ACTH for four months and is well, carrying a full schedule at Boston University. His vital capacity is now 3.2 liters, and his X ray dated September 12, 1955 reveals some residual fibrosis in his right lung, but represents a marked improvement over films taken a year previously.

This patient raises several points for consideration. Selye[9] has shown that *inflammation localizes the action of an irritant or toxin. If the toxin is* one which by spreading may be lethal to large areas of neighboring tissue, inflammation serves a useful purpose by putting up a barrier. On the other hand, if the irritant is not terribly damaging but stirs up a lot of inflammatory response, especially in the lung, the inflammation itself may be more threatening to life than the irritant.

It would seem that in the case of crude oil #5 the latter condition prevails. It may also prevail for other hydrocarbons lower on the scale of *toxicity, such as mineral oil. In the case* of the more acutely damaging hydrocarbons, such as gasoline and kerosene, a question remains as to whether inflammation serves a useful or detrimental role and as to whether its suppression by *steroids is indicated or not. This is a question which probably*

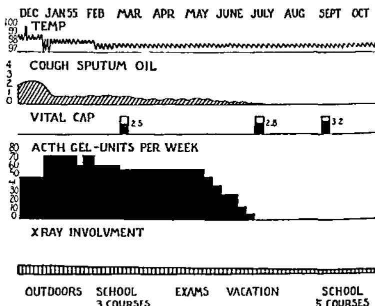


CHART IV

can be solved by animal experimentation and possibly by the use of cortisone in some desperate human clinical example of kerosene poisoning—of which there are still far too many occurring especially in rural areas among small children [5]

This case suggests the probable usefulness of steroids in treating other industrial accidents involving similar products and also their possible usefulness in merchant seamen and sailors who are subject to aspirating crude oils in sea disaster and who have been thought hitherto to die of exposure

A final question is raised as to whether these hydrocarbons will eventually prove to have a carcinogenic effect on the pulmonary tissue to which they were so long exposed I would welcome opinion on this point

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DISCUSSION

Dr Theodore I Badger (Boston) There is probably no parallel but it is very interesting to observe that in bailing out a severe asthmatic 200 mg of cortisone per day are necessary for an average of five or six days in order to get a diminution and disappearance of symptoms It is interesting to note here that while this patient was treated with smaller doses of the steroid he made some improvement and although the type of disease is entirely different it is important here that when he was started with big doses of first one and then the other he showed his first real improvement

Dr Richard A Kern (Philadelphia) I should like to ask whether broncho copic aspiration was attempted during the early days of his illness

Dr Walter Palmer (Chicago) I want to add a note to Dr Badger s comment with respect to bailing out and dosage

In terms of the amount of steroid we have found it necessary to use in extreme situations in ulcerative colitis 300 mg of cortisone is not a big dose

Dr Henry M Thomas Jr (Baltimore) I would like to comment on just one small point Dr Graham mentioned pneumonia produced by other oils bland ones such as mineral oil

We have encountered I think five cases now We reported the first one of an inhalation oil pneumonia which was a very benign disease in fact asymptomatic and discovered only through accidental x ray then thought to be a tumor of the lung and removed surgically at which time it was found to be an oil aspiration granuloma A lipoid cell pneumonia if you like which is somewhat different and in which the oil is not coughed up except in small amounts mostly remaining and producing a chronic inflammatory disease but nothing similar to this case of yours

Then also I was fascinated by this very good first slide which you showed and I wondered how the one nostril happened to stay out of water That was a very fortunate thing

Dr John R Graham (Closing) Dr Thomas we had to reconstruct the story of what happened to this man from a description as given by the firemen who rescued him All I can say is that this was their description It was extremely fortunate and gave him a 50 per cent chance

I am also interested in your mentioning the pneumonia resulting from the inhalation of a more benign type of oil

It is difficult to find too much about this sort of thing in the literature but one does get the concept that the more volatile the product of the fractionating petroleum column is the more toxic it is when applied to pulmonary tissue

I was particularly interested to find out how prevalent kerosene poisoning is in the rural areas Apparently in some areas it is the most common cause of death from accidental poisoning among children Quite a large series of cases have been collected in some hospitals over the course of two or three years with a mortality ranging from 2 to 9 per cent There are some other series in which there are no cases which I

Kero ene p n oning especially if the kero ene is a pirated into the lungs can be a very acute and even fatal di ease There is interesting nimal experimentation which has been done which more or less goes to show th it the toxicity of the kero ene comes when it gets into the lung by direct aspiration or by aspiration of vomitus containing kero ene and that the coma and central nervous ystem involvement result from ab orption from kerosene that gets into the intestinal tract A baby may take as much as a pint by mouth and if he does not cough or get it into hi lungs m iy suffer no serious consequences except drowsine while as much a a te i poonful getting into the bronchi may prove to be fatal

I would like to make one point because actually it is kero ene poisoning I find my elf mo t interested in in studying this case One of the features which has come out *in that disease is that contrary to the usual procedure* in treating a ca e of poisoning it would become apparent that perhaps it is better to leave the kero ene in the stomach of the child who has inge ted some rather than try to wash it out becau e about 50 per cent of children vomit in the proce s of gastric lavage and then get the kero ene into their bronchi where it causes po ibly f tal damage to pul mon iry tissue I have even wondered whether thorazine might be u ed in small qu intities to prevent spontaneous vomiting

In respon e to Dr Kern s question the patient was not bronchoscoped I would gather that in the first week at the Boston City Ho pital he was just too ick to do almo t anything with He was very critically sick more so than the chart would suggest

When he was brought to our ho pital we felt that perhaps the time had gone by We beg in to change our minds about that and worry about whether we *should or* should not bronchoscope him We ended up by not doing o We tried all sorts of other measures inhalation of isoprel and administration of mists with pancreatic enzymes and all that sort of thing But we felt that none of tho e measures really produced any ignificant effect

As for Dr Badger s and Dr I almer s comments on the dosages of corti one I am ure we should have given the patient more the fir t time we tried it It was quite obvious that he wa not getting enough and a we reduced it his symptoms all returned with increasing vigor It was only when we u e l con iderably larger amounts that we got the de ir il le clinical effect

THE MECHANISM OF ASTHMA AS REFLECTED BY THE RESULTS OF TREATMENT

Abstract

By FRANCIS M. RACKEMANN, M.D.*

BOSTON

In the asthma of children and young people, a sensitiveness to a foreign substance in dust or food provides a satisfactory explanation of the illness in 82 per cent of the cases. The exciting cause of asthma is outside the body — *extrinsic*. In the next older age group, "asthmatic bronchitis" is a descriptive term which indicates that the primary allergy may be complicated by infection. The symptoms occur in isolated attacks after colds. In another group, however, the infection itself is adequate to explain the clinical picture; the patient is hypersensitive to the organism—the mechanism depends probably upon a "bacterial allergy."

The asthma which begins after age 40 has been called "intrinsic," which means merely that the exciting cause is something which the patient carries within himself. Infection is the most common cause, but psychic factors play a part in most of the cases. They are dominant, however, in only about 10 per cent. Other factors, including improper habits of living and eating, are dominant in about 20 per cent. The fact is that classification according to the exciting cause is unsatisfactory, because mixed causes are the rule.

The fact that about a third of all cases of intrinsic asthma become clear of symptoms after a time indicates that the process is reversible, and that shows that the cause depends on a disturbance of function rather than of structure. Arguments for and against the factors of infection and of psychogenic causes lead to the general conclusion that neither one, nor even both together, can explain all the cases, and that means that there must be *still another factor not yet understood.*

The patient has a "weak spot"—a "low resistance"—which makes him react with asthma when stress and strain of any kind comes upon him. In 1945 R[1] discussed "depletion" as a vague circumstance which might describe the condition. It was somewhat comparable to the alarm reaction which Selye suggested might be concerned with adrenal function. It is interesting to regard all the reversible chronic diseases as reaction patterns resting on a background of susceptibility. The idea is the same as Dr. J. S. L. Browne's[2] concept of the iceberg with its peaks above water repre-

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senting the different symptom complexes and with its larger mass below representing the background Specific treatment, like desensitization lowers one or other of the peaks but more general treatment like ACTH and the steroid hormones lowers the iceberg as a whole Whether the background—the iceberg mass—is common to all the peaks or is specific for each symptom complex is still an open question If we could know the nature and origin of the background we could understand how the patient happened to develop his asthma and then a treatment applicable to all the cases would become available and the asthma problem would be easier to solve

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DISCUSSION

Dr Robert L Levy (New York) I shall leave the discussion of asthma to those who know more about it than I do But I cannot resist the temptation to remark that Dr Rackemann's presentation illustrates once again the fact that from careful clinical observation and long term follow up there is still much to be learned

Dr Walter S Burrage (Boston) May I reinforce what Dr Levy said about this very interesting presentation In addition I wish to point out that no one in the United States has been able to approach Dr Rackemann in his ability and tireless industry in demonstrating the importance of long term follow up in all types of allergic disease

Dr F Tremaine Billings Jr (Nashville) We have had an opportunity on several occasions to have the good fortune to be visited by Dr Rackemann in Nashville and I remember very vividly one visit he made

We usually give a visitor a rather hard go around in the morning I remember that one of the house officers had been trying to get at him Shortly before the rounds were over he finally was able to say Dr Rackemann we have a very resistant long term intractable asthmatic up on the Negro ward We would like to have a minute of your time to see this man

Dr Rackemann said I would be very happy to see your patient but I believe I will have to devote about three hours to him

I think this is appropriate in relationship to the fact that Dr Rackemann does not spend three hours with his patient he spends thirty years with them [Laughter] I think this is probably the secret of his success Not many of us have experienced such wonderful success in the management of asthma as Dr Rackemann has

Dr John S Lawrence (Los Angeles) For the record I would like to mention two procedures or methods of therapy that have in my experience been associated with a clinical cure I am quite sure that Dr Rackemann has heard of them but did not mention them because of lack of time

One is a preparation which was made down in Rio Grande Valley and whose name I do not know A patient of mine who was the wife of a doctor obtained it

some years ago took it and to my surprise, pleasure and chagrin has never had any more trouble with asthma

Second there is a clinic in Mississippi where a patient (also a confrere of mine) went for intractable asthma No one had been able to relieve him and for this reason he decided that he would give the clinic a trial He consulted me about it I told him that I had exhausted my resources and consultant and to go to the clinic if he wished

He came back some three years ago He had not had any more serious trouble with asthma The patient admits it could be psychic but he is not concerned about that—the important thing to him is that he no longer has serious trouble with asthma

DR WALTER L PALMER (Chicago) This was a fascinating presentation I would like to ask a question with respect to failure I have been impressed with the treatment of certain acute very ill asthmatics with intravenous ACTH Are there instances in which it does not succeed in bringing about a temporary remission?

DR FRANCIS M RACKEMANN (Closing) I appreciate all the kind remarks of my friends

Dr Billing wanted to know about the method of follow up Most of our information came from letters Whereas about a third of the patients reported themselves as relieved of their asthma it is interesting to find that in many cases this relief came not immediately after the treatment but came some time later on Such reports make it hard to claim any direct effect of the treatment itself

I do not know what happens down on the Rio Grande but I do know something about Biloxi Mississippi That is where the patient puts his money on the barrel head stays a few weeks and gets well And that reminds me of what I saw in France in June 1950 In that year the European Congress of Allergy met at Le Mont Dore a lovely little town in a valley between the hills where for many years—centuries perhaps—the sulfurous water coming from a spring had been recognized as good for asthma A beautiful building had been erected over the spring and here came asthmatic patients from all over Europe to have the nasty smelling water administered through every orifice In sprays douches enemas and baths the water was given and a prescribed quantity was swallowed

All the patients did well in Le Mont Dore as they did well in Biloxi and why was that? I had to be cautious in my skepticism about the sulfur water but I emphasized that the patient were staying in a very attractive place where life was easy and quiet They had escaped from whatever it was that was causing trouble at home They had a low resistance

It is easy to talk about low resistance whether one means low resistance to infection or low resistance to anxiety or to fear or simply to fatigue or perhaps low resistance to the marital partner Low resistance is the background of asthma and some day we will learn what it is

Dr Palmer wants to know about failures from ACTH Of course there are failures ACTH does not cure everybody but it does relieve a high percentage I can add this Dr Burrage's lady who died of asthma was pumped full of ACTH with Dr George Thorn helping in the process The problem is still open

CLUES TO BETTER UNDERSTANDING OF THE NATURE AND TREATMENT OF CERTAIN INFECTIOUS DISEASES

By THEODORE E. WOODWARD, M.D.

BALTIMORE

In spite of notable advances in the clinical and antimicrobial management of important infectious diseases, i.e., rickettsioses, meningitis, pneumonia, septicemia, endocarditis, cellulitis, plague, enteric disease and others which have reduced drastically the incidence of death in pediatric and adult patients, mortality has not been erased nor have important residual tissue changes been totally reversed. Pathogens causing many of the important diseases may, on occasion, elude detection in the early stages of illness and, if proper specific therapy is withheld, may attack the tissues so rapidly as to outdistance treatment. Not infrequently a patient may die, bacteriologically cured. A therapeutic paradox. Expressed in another sense, what is the underlying basis for toxemia? Patients are described as being toxic and yet information is lacking as to how a pathogenic agent alters the tissues or unalterably damages a cell beyond repair with resultant clinical toxemia and death.

There has been a reawakening of interest in the more fundamental nature of infections now that the virtues and limitations of chemotherapeutic agents have been recognized. Except for certain notable exceptions, such as infections caused by staphylococci, *Proteus vulgaris*, resistant streptococci, pyocyaneus and a few others, the therapy of many infectious processes presently amenable to control leaves little room for improvement. Death in meningitis, pneumonia, rickettsioses, plague, septicemia and other diseases usually is attributed to irreversible tissue changes that have transpired prior to the administration of the effective chemotherapeutic agent. It is now necessary to characterize fully the underlying biochemical and physiological disturbances that have been involved by the offending microorganism or its toxin. Once the nature of these underlying alterations within the cell is known, supportive care on a more fundamental basis may be instituted. With little stretch of the imagination, one can envision the future treatment of serious infectious processes by (1) administration of an antibiotic for microbial control and (2) the administration

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This study supported by a grant-in-aid from the Parke Davis Company, Detroit, Michigan.

of an essential metabolic substance or substrate necessary for proper cell function Only enlightened research in these fields will provide the clues to these mysteries Dubos[1] is one of the current leaders who has rekindled interest in biochemical determinants of infection

Certain pertinent clinical therapeutic and physiologic problems serve to illustrate these trends Model chosen for discussion are the rickettsioses epidemic hemorrhagic fever meningococcal infection and important diseases of the gram negative group

I *Role of Capillaries and Small Blood Vessels in Pathogenesis of Disease*

Epidemic hemorrhagic fever a serious illness first attacked American soldiers in Korea during the fall of 1950 This illness characterized by fever of five to seven days headache myalgia and a bleeding tendency with petechiae in the skin mucous membranes and in serious case the kidney musculature of the right atrium lungs pituitary adrenals and elsewhere often led to death Renal failure with shutdown proteinuria and azotemia was a common accompanying feature

During the course of the illness which in the severely ill lasted two to three weeks shock developed on about the fifth day During the shock hemodynamic studies revealed relative hypovolemia and death could be delayed for a short time by copious administration of adrenergic drugs such as norepinephrine Following abatement of the shock phase however the patient might develop a relative hypervolemia and may die as a result of pulmonary hemorrhage edema or bleeding into other vital organs The etiologic nature of this illness has eluded detection In spite of these disappointments including the failure to develop a satisfactory specific chemotherapeutic agent observations of the physiologic changes of blood vessels led to an important tributary of knowledge

Greisman noted that the capillaries of the nail bed in the shocked patient were dilated and that the motion of red blood cells (vasomotion) was sluggish The reaction abated with normal vasomotor tone returning as convalescence began

On inoculation of plasma from the shocked patient into anesthetized rabbits vasodilatation with sluggish motion was noted in capillaries in about one minute and continued for approximately ten minutes The effects of this vasoreactor substance could be blocked in animals by the administration of cortisone antihistaminic drugs (Benadryl) of plasma from convalescent patients

Wiseman and Greisman[3] subsequently demonstrated that this type of vasoreaction was not specific for patients with epidemic hemorrhagic fever but occurred when plasma obtained from patients starved for 24 hours was inoculated into the experimental animal Furthermore these observers

noted that the prior administration of glucose to the hemorrhagic fever patient or the fasted volunteer would negate the vascular response

A vasoreactive fraction is present in the plasma of humans sufficiently potent to dilate the terminal capillary vessels of animals provoke stand still of blood flow, produce tissue edema and ultimately cause death The precise nature of this material has not been elucidated The phenomenon may actually represent an ill defined immunologic blood reaction which may fluctuate with the nutritional state of the host and hence may not represent the presence of a specific circulating vascular toxin While the idea of a specific circulating hematotoxin remains a plausible one the experience in epidemic hemorrhagic fever serves to emphasize the difficulties encountered in differentiating this hypothetical toxin from the complex vasoreactive substances of immunologic and endogenous origin[3]

Wattenburg et al[4] have succeeded in demonstrating potent vasoreaction by inoculating a rickettsial toxin into mice Following intravenous inoculation of toxin direct observation revealed that arterioles were greatly reduced in caliber pre capillaries disappeared from view vasomotion accentuated and tissue edema resulted from leakage of plasma from the circulatory system

These observers showed concurrent hemoconcentration (increased hematocrit) as a result of plasma loss Utilizing tracer substances (Dextran and an azoprotein T 1824 albumin) leakage of plasma was demonstrated with edema throughout most of the tissues including the muscle pancreas kidney heart etc all indicating extensive increased permeability and capillary leakage The extravasation of plasma from the intravascular compartment into the tissues as a result of the rickettsial toxin is striking

Although the mechanism is unknown it would appear that rickettsiae or toxin exert their effect by direct action on endothelial cells[4] During the spring and summer of 1954 Liu[5] demonstrated a similar vasoreactor effect in mouse capillaries following the inoculation of whole untreated plasma from patients acutely ill with Rocky Mountain spotted fever Increased vasomotion with venous dilatation stasis and edema of subcutaneous tissues was demonstrated as shown in figure 1

The problem as to how rickettsia or its toxin acts upon blood vessels is unknown but the mechanics seem clear This vasomotion and capillary permeability provides a supplementary explanation for the early and late vascular manifestations in Rocky Mountain spotted fever

It is a striking fact that antibiotic treatment if given sufficiently early will arrest these vascular defects apparently by arresting rickettsial growth and subsequent toxic changes

The toxic action by rickettsiae on capillary endothelium may involve alteration of essential metabolic pathways Wisseman et al[6] have demon

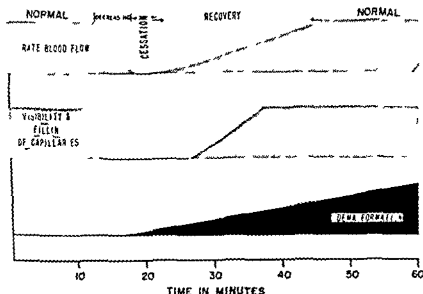


Fig 1 Vascular phenomena observed in mouse skin after intravenous injection of plasma from Rocky Mountain spotted fever patients (Reference 5 Liu P S J et al)

strated that suspensions of *Rickettsia mooseri* may oxidize glutamic acid through pathways involving alpha ketoglutamic succinic fumaric malic oxalacetic and pyruvic acid Rickettsiae conceivably may compete with their host cell for the Krebs cycle intermediates to such an extent that capillary damage might result from diminished production of high energy phosphate bonds Greiff and Pinkerton[7] have shown that rickettsiae multiply rapidly in a medium of low oxygen tension particularly in the tissues of fertile eggs when respiratory enzymes such as the cytochromes have been blocked by cyanide On the other hand a respiratory catalyst such as methylene blue which may by pass the cytochromes suppresses rickettsial growth

Although patients now rarely die from clinical rickettsioses the shortening of the course of disease in late cases remains a challenge Undoubtedly a clearer understanding of physiological abnormalities in the capillaries and elucidation of the intermediary metabolic aspects will provide the basis for even sounder supportive therapy

II. *Persistence of Microorganisms in the Host and the Relapse Problem*

Various microorganisms reside in tissues of the human host without causing overt manifestations of illness. Examples include the rickettsiae in Brill's disease, typhoid bacilli and the typhoid carrier state, plasmodia of malaria and numerous viral agents of which herpes is a prime example.

Recently, *Rickettsia rickettsiae*, the causative agent of Rocky Mountain spotted fever, was isolated from the lymph tissues of a convalescent patient 14 months after subsidence of the acute infection.[8] This ability of viable rickettsiae to reside in the tissues of convalescent patients months after the active infection has been demonstrated in scrub typhus[9] and epidemic typhus.[10] Zinsser hypothesized that Brill's disease was recrudescent typhus fever caused by rickettsiae that had resided in the host for years after the initial illness. Thus latent or inapparent infections may remain unnoticed, yet for reasons not understood this equilibrium may be upset and active disease develop.

It is of interest that the last three cases of Brill's disease (recrudescent typhus) which occurred in Baltimore demonstrated a dual factor implicating a stress phenomenon. Historically, each patient had typhus fever in Europe at least ten years previously. Each developed fever, headache, rash and other classic features of recurrent disease while convalescing from a surgical procedure, i.e., thyroidectomy,[11] paronychia requiring incision,[1] and cholecystectomy, respectively. Why should these latent rickettsiae suddenly escape their confines within the cell and again provoke disease? Similarly, quiescent malaria is frequently reawakened following surgical trauma or superimposed infection.

Price has succeeded in causing recurrent rickettsial infection through stress mechanisms.[10] In primates experimentally infected with rickettsiae, second infection is provoked months later by administering large doses of corticoids. The recurrent disease cannot be ascribed to reduction of antibody by hormonal influence. Important clues are to be found here since the nature of these phenomenon are poorly understood. Dubos emphasizes that accumulation of lactic acid in tissues from inflammatory exudates exerts potent bacteriostatic and bactericidal action in contrast to accumulated keto acids which favor infection.[1] Possibly similar factors of altered metabolic equilibrium account for the renewal of rickettsiae and other microbial infection.

Recrudescence of clinical infection soon after the subsidence of active disease poses a problem of more than academic interest. In patients with rickettsioses, typhoid fever, tularemia and brucellosis (intracellular parasites), specific therapy may arrest the manifestations of illness, yet if the timing is faulty, a relapse may ensue.

When patients with scrub typhus fever, ill for five days or more, are

treated with suppressive antibiotics acute manifestations usually abate within 24 hours and convalescence is uneventful whether specific therapy is continued for a week or as briefly as one day.

However, when patients with the same rickettsial disease are treated early in the course of infection before sufficient antigenic stimulation and immunity have ensued, relapse will occur and rickettsiae are readily reisolated from the blood.

By proper spacing of antibiotic therapy through intermittent regimen relapses may be prevented.[13]

The relation of immunity in rickettsial diseases and time of therapy may be summarized in figure 2.

Under situation A, relapses do not occur when specific treatment begins on or after the sixth day of disease regardless of duration of treatment. However, when treatment is given quite early, such as the second febrile day, relapse ensues approximately eight days after cessation of treatment. Situation C is a graphic presentation of the findings in a human trial in which rickettsiostasis by daily antibiotic treatment was maintained for 28 days after an artificially induced infection. Suppressive antibiosis for 28 days allowed insufficient time for immunity to develop

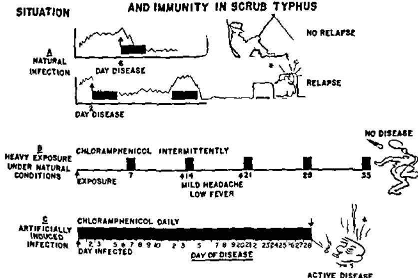


FIG. 2. Relationship of chloramphenicol action and immunity in scrub typhus. (Reprinted from Dynamics of Virus and Rickettsial Infections, Blakiston Co., 1954, page [illegible].)

under these conditions and full blown active disease occurred in this group.

In situation "B" it is noted that the intermittent administration of chloramphenicol at seven day intervals in naturally infected human volunteers permitted the host to develop his own defense. Continuation of these intermittent courses up to the thirty fifth day prevented the disease from appearing in the active sense. The mild headache and low grade fever noted just prior to several of the intermittent doses were undoubtedly manifestations of infection. At these times *Rickettsia orientalis* were readily isolated from the patient's blood. Immunity, therefore, appears to be dependent in large part upon the mass of antigenic stimulation and resultant immune response.

Similarly, typhoidal relapses are noted more frequently in our current chemotherapeutic era. The 10 per cent relapse rate formerly experienced by Osler now approaches 20 or more per cent.

Relapse in typhoid fever usually occurs 15 days after the antibiotic is discontinued. Our concepts of drug administration in typhoid are similar to those in early rickettsial infection,[14] that is, intermittent application of the antibiotic with clinical suppression at crucial periods and rest periods allowing antigenic stimulation with bacterial multiplication with subclinical disease during the treatment interval. This regimen is demonstrated in figure 3.

An additional method of providing antigenic stimulation is the administration of killed typhoid vaccine as shown. Marmion, a British investigator, on the basis of a large series of cases studied, is convinced of the value of this combined regimen.[15]

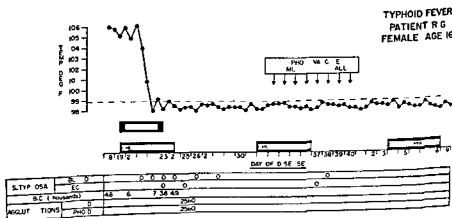


FIG 3 Regimen of intermittent chemotherapy and vaccine in patient with typhoid fever. Cortisone administered for anti toxemic properties.

The ameliorating action of cortisone against the typhoidal toxin has been demonstrated under certain conditions in the experimental animal and its value as an antitoxemic agent in treatment of the human disease has been shown.[16, 1]

Thus appropriate chemotherapy does not succeed in eradicating the microbe from the host; the same microbe may reemerge from the confines of the cell at a later date and in the presence of waning or insufficient immunity again provoke disease. Immunity apparently comes at a price dependent upon the degree of antigenic stimulation and host reaction that has transpired by the time specific therapy is instituted. One does not interfere too greatly with the natural evolution of immunity if the timing is accurate.

III *Nature of Underlying Lesion*

Certain microbial diseases are characterized by distinctive and occasionally explosive dermal reactions, i.e., rickettsioses, meningococcal infections, septicemia and others. Although the histological features of the lesions have been described, the nature of the altered physiochemical environment leading to their development has not been clearly elucidated. Histologically the vascular lesions of small and medium sized blood vessels in periarteritis nodosa and the vascular nodule of rickettsioses bear some resemblance. In periarteritis nodosa, a disorder thought to arise as a result of hypersensitivity to various stimuli, there is endothelial swelling, cellular infiltration, fibrinoid changes and necrosis with eventual thickening of the entire vessel.

Similar histological features characterize the lesion of Rocky Mountain spotted fever. The endothelial cell is swollen (rickettsiae multiply intracellularly in the intimal cells), the muscular layer is fragmented with necrosis and there is a florid proliferative reaction encircling the vessel. Platelet and leukocyte thrombi occur in periarteritis nodosa as well as in the rickettsial lesion.

Some investigators have been impressed with the similarity of the dermal lesions found in certain systemic microbial diseases and those in the experimentally produced Shwartzman reaction. The skin manifestations of meningococcemia fall into this category.[18, 19] The Shwartzman reaction is brought about by inoculating a culture filtrate from certain gram negative bacteria intradermally. Local dermal inflammatory response at this site is produced by the intravenous injection of the same or other culture filtrates 24 hours later. Hemorrhage into the skin and necrosis does not develop until after the intravenous or provoking injection of toxin. The reaction in the prepared area has been attributed in part to leukocyte and platelet thrombi within small blood vessels.[19]



Fig. 4. Rocky Mountain spotted fever. Vascular lesion in arteriole showing intravascular *thrombi* of leukocytes, endothelial swelling, and perivascular cellular proliferation.

The *generalized* Shwartzman reaction occurs when rabbits are given two successive intravenous injections of gram-negative bacterial endotoxin and consists of hemorrhagic necrotizing lesions in various organs, particularly the kidney (bilateral cortical necrosis).[18, 20, 21] This reaction is apparently *motivated* by circulating polymorphonuclear leukocytes since the reaction may be blocked by nitrogen mustard. Small *blood* vessels are occluded by eosinophilic material resembling fibrinoid. Platelet and leukocyte thrombi are likewise demonstrated. Thomas et al.[22] employ this model to study the pathogenesis of the rheumatic lesion.

Recently, we observed a male youth on the second day of illness with all the clinical features of meningococcemia, i.e., fever, headache, meningeal signs and purpuric rash.

Meningococci were isolated from a skin lesion. The meningitis and general manifestations of illness subsided rapidly on appropriate chemotherapy. In spite of dramatic general improvement, however, mild low grade fever persisted and several skin lesions over the ankles and knees trebled in size, becoming hemorrhagic and necrotic and formed indolent, slow healing ulcers. Culture of these lesions failed to reveal pathogenic bacteria.

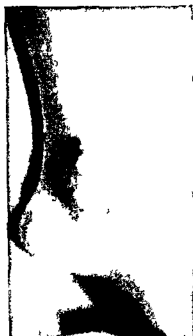


Fig 5



Fig 6

Fig 5 Meningococcemia Purpuric skin lesion prior to chemotherapy Meningococci isolated from skin blood and spinal fluid

Fig 6 Meningococcemia Same lesion as shown in Figure 4 Note extensive area of necrosis undergoing granulation and epithelization Similar non pyogenic Shwartzman like lesions occurred in other sites

Conceivably these lesions developed as a result of a Shwartzman like reaction following release of antigen coincident with chemotherapy the latter serving as a provoking stimulus to some of the already sensitized dermal areas This type of reaction readily producible in rabbits with meningococci is rarely seen in human meningococcal infections Why it occurred in this particular patient is unknown In cortisone treated rabbits inoculated intradermally or intravenously with bacterial toxin extensive hemorrhagic lesions of the dermal and generalized type have been noted [20, 21] Similar clinical findings have not been reported in meningococcemia after cortisone therapy The patient described above did not receive cortisone

The dermal hemorrhages of seriously ill patients with Rocky Mountain spotted fever and epidemic typhus resemble those of meningococcemia Developing more insidiously over several days the lesions become purpuric extensive and ultimately slough to form indolent ulcers and subsequently scars



Fig 4 Rocky Mountain spotted fever Vascular lesion in arteriole showing intravascular thrombi of leukocytes endothelial swelling and perivascular cellular proliferation

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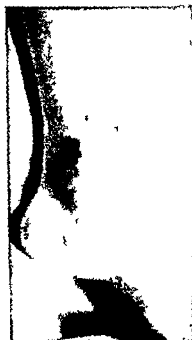




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Rickettsiae multiply in the capillary vessels of all organs including the skin A rickettsial toxin probably is dispersed intravenously and conceivably the extensive vascular abnormalities which lead to necrosis may occur as a result of a Shwartzman like phenomenon One cannot disregard the direct action of rickettsiae upon the endothelial vessel particularly in the capillary

IV *The Problem of Plague as Related to Time of Therapy and Toxemia*

Pneumonic plague a disease of antiquity elucidates why trends of management must differ from the conventional antimicrobial approach Plague caused by *Pasteurella pestis* is manifested frequently by a bubo which may subside uneventfully without too severe general reaction although the overall mortality in untreated bubonic plague is 30 per cent

Occasionally the bacillus escapes the confines of the lymphatic system and produces a virulent and rapidly fatal septicemia Patients with the septic type may develop a secondary pneumonia before death and spread plague bacilli via droplet routes Pneumonic plague so produced is rapidly fatal usually within 40 to 72 hours after the onset of illness

Treatment of this highly fatal disease with broad spectrum antibiotics or streptomycin prior to the twentieth hour of illness uniformly results in recovery [3]

Of equal interest is the record of the following patient who succumbed to plague pneumonia Specific treatment was not instituted until after the thirtieth hour of disease In spite of prolongation of life for 36 additional hours death occurred The striking feature of the autopsy was the failure to demonstrate viable *P pestis* in suitable bacteriologic preparations from the lung or liver—death with bacteriologic cure

This and similar situations emphasize the need for better understanding of the true nature of the underlying infection The plague bacillus elaborates a potent toxin which exerts profound changes on blood vessels resulting in necrosis with small and extensive hemorrhages

P pestis produces a fibrinolysin which may contribute to the hemorrhagic tendency The toxin possesses potent neurotropic properties Reliable data relative to the metabolic defect provoked by the plague bacillus or its toxin is not presently available Cortisone of demonstrated value in ameliorating the toxemia in typhoid fever and scrub typhus in limited trials has failed to alter significantly the course of plague patients late in their disease [23] Hyperimmune serum has likewise been ineffective Certainly the gross lesions in the fatal case are not as extensive as physicians are accustomed to observe in many fatal illnesses Conceivably a metabolic defect remediable by appropriate biochemical replacement is a sound prophecy

CASE NO 8 RAZANAMANANA F 30 40 K
LAZARET D AMBOHIMIANDRA
TANANARIVE

TEMP DEG C. — 41, 40, 39, 38, 37 — DEATH 4 AM

CHLORAMPHENICOL GRAMS / DAY — 4.0, 2.0, 0 — TOTAL 7.5 GM

BLOOD CULTURE	—	—				
LEUKOCYTES/MM^3	15 400					
ANIMAL INOCULATION	+ +	— —				
SPUTUM CULTURE	+ +	—				
DAY OF DISEASE	2	3	4	6	6	7

Fig 7 Pneumonic plague Course of illness in fatal case first treated on second day of disease (Reprinted from American Journal of Medicine 14 89 195)



Fig 8 Human plague Extreme vascular changes showing hemorrhage and necrosis in renal cortex of fatal case Note interstitial extravasation of blood and tubular necrosis

Rickettsiae multiply in the capillary vessels of all organs including the skin. A rickettsial toxin probably is dispersed intravenously and conceivably, the extensive vascular abnormalities which lead to necrosis may occur as a result of a Shwartzman like phenomenon. One cannot disregard the direct action of rickettsiae upon the endothelial vessel particularly in the capillary.

IV. *The Problem of Plague as Related to Time of Therapy and Toxemia*

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Occasionally, the bacillus escapes the confines of the lymphatic system and produces a virulent and rapidly fatal septicemia. Patients with the septic type may develop a secondary pneumonia before death and spread plague bacilli via droplet routes. Pneumonic plague so produced is rapidly fatal usually within 10 to 72 hours after the onset of illness.

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40
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DEATH 4 AM

CHLORAMPHENICOL GRAMS / DAY

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TOTAL 7.5 GM

BLOOD CULTURE	—	—				
LEUKOCYTES / MM³	15,400					
ANIMAL INOCULATION	+ +	— —				
SPUTUM CULTURE	+ +	—				
DAY OF DISEASE	2	3	4	5	6	7

Fig. Pneumonic plague. Course of illness in fatal case first treated on second day of disease. (Reprinted from American Journal of Medicine 14 2[illegible] 19[illegible]3)



Fig. 8 Human plague. Extreme vascular changes showing hemorrhage and necrosis in renal cortex of fatal case. Note interstitial extravasation of blood and tubular necrosis.

Problems related to understanding basic tissue alterations in infectious diseases are broad and complex dependent upon a host of factors i e host reaction character of the invading parasite and numerous intermediate considerations The present discussion has neglected many vital contributions now under intense consideration by numerous investigative groups The requirement for iron in metabolic substrates has been shown to be a variable and *important factor in the production of diphtheria toxin* probably through interference with respiratory enzymes such as cytochrome B of *Corynebacterium diphtheriae* [4, 5] Techniques developed by Coons have led to better detection of the offending antigen in tissues during the early stages of infection [6] By tagging antibody with tracer or fluorescent stains and through utilization of proper photographic techniques antigen may be detected within the host cell Properdin [7] a recently characterized component of normal plasma has been identified as a euglobulin possessing potent bactericidal properties

These and many other noteworthy contributions in the immunological field will undoubtedly better clarify the nature of heretofore unexplained mysteries

Conclusions and Summary

Many microbial diseases are now amenable to control as the result of drug action which denies the causative germ of an essential metabolite necessary for its growth Sulfonamides rob the microbe of para amino *benzoic acid penicillin is thought to impede bacteria life by denial* of glutamic acid and other essential substances

So little is known of the metabolic alterations which pathogenic organisms effect in the tissues Vital mysteries are concerned with the metabolic substrates which determine whether a microorganism may invade and cause disease reside latently in a host cell or die Once invasive what are the physiochemical alterations in the tissues which really account for the course of events?

Certain trends that investigation in infectious diseases must pursue are

1 The vascular system and particularly the capillaries contributes to the pathologic physiological tissue alterations in infectious diseases i e epidemic hemorrhagic fever rickettsioses meningococcal infections plague etc To understand infectious disease processes it is necessary to clarify the nature of increased capillary permeability

2 Potent vasoreactor substances capable of bringing circulation to a standstill in the capillary bed are present in the plasma of patients with infectious disease and also in the normal individual under certain conditions Much clarification is needed

3 The toxins of rickettsiae meningococci (in the broad sense) and plague bacilli possess potent vascular factors

4 Microorganisms reside in the human host long after the initial infection They may again provoke illness when the proper environment in the host is created The nature of this environment is unknown

5 Specific therapy administered for a short time to patients early in the course of scrub typhus may result in relapses Relapses are common in typhoid fever and other diseases caused by gram negative bacteria Interrupted or discontinuous therapy may prevent recrudescence Combined vaccine chemotherapy may have much in its favor in certain instances

6 Skin lesions of rickettsial disease and meningococcemia resemble the Shwartzman lesion

7 The biochemist and physiologist along with the microbiologist immunologist and clinician hold the key to the box of clues to the true nature of infectious disease

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DISCUSSION

DR WORTH B DANIELS (Washington D C) Dr Thomas makes an accusation He and I argued hard and long on some of these points and maybe he was right about toxemia *I think he was wrong about the value of meningococcus antitoxin* After the advent of sulfonamides its use was superfluous

I have seen local gangrene in instances of meningococcic bacteremia and one instance of loss of an arm from arterial thrombosis

I think Dr Woodward is reaching some fundamental new knowledge of infection which *will help us to understand many obscure points*

In 1947 I reported before the Climatological 300 patients who died of meningococcic disease Of that group 52 per cent died of bacteremia without meningitis Forty two per cent died with Waterhouse Friedericksen syndrome and 10 per cent died with fulminant bacteremia without adrenal hemorrhage Many of the latter group had all *the clinical manifestations of Waterhouse Friedericksen syndrome* except that at autopsy their adrenals appeared to be normal The capillary and vascular changes in those patients were striking They had extremely extensive purpuric and hemorrhagic rashes indicative of broad spread capillary damage They

had hemorrhagic areas in the pleura pericardium myocardium lungs intestines evidence of diffuse vascular damage—the disturbance Dr Woodward has brought to our attention

I have recently lost a patient with Waterhouse Friedericksen syndrome sixty hours after treatment was begun and after the temperature was normal and cultures of the blood sterile At autopsy wide spread vascular damage was evident and there was hemorrhage in both adrenals but cultures of heart blood and cerebro spinal fluid were sterile The patient had been cured of infection but died of vascular injury

Dr Stewart Wolf (Oklahoma City) Dr Woodward would you comment on the possible relationship of your studies to those of Knisely? Could Knisely's sludging be a stage in the continuum of the process which you describe?

Dr A Murray Fisher (Baltimore) It was a very interesting talk and certainly covered a good deal of ground I believe that Dr Woodward is on firm ground when he discusses the problem of the reaction of the tissues and the cells of the patient to the infectious agents

Going back to his model of the plague infection in humans where the patient has died in spite of bacteriological cure I was wondering if he had been able to demonstrate any evidence of immunity due to the infection in such a case It would also be interesting to know whether or not he has performed any animal experiments in which he has been able to show similar effect with this bacillus

Dr Theodore E Woodward (Closing) Thank you Dr Daniels Dr Wolff and Dr Fisher for your remarks

Dr Daniels I take pleasure in informing you that many members of our senior class have read your paper on the cause of death in meningococcal infections which appeared in the *American Journal of Medicine* it provides excellent statistical information

Knisely s studies on sludging cited by Dr Wolff are pertinent to this discussion on intravascular reactions In the rabbit inoculated with horse serum sludging within the capillaries occurs (Ebert and others) This sludging phenomenon is not significantly altered by cortisone treatment

It was stated in my very rapid transit of the data presented that the underlying mechanisms of the changes in vasomotion and altered capillary permeability were not clearly understood and that an abnormal immunological blood reaction may be responsible

Dr Fisher in patients with pneumonic plague who succumb to the infection death ensues before antibodies have appeared in measurable titer Those patients successfully treated develop agglutinins and neutralizing antibodies

The question of using killed antigens for therapy of specific infections has been raised There is some evidence that killed typhoid vaccine given during early convalescence is beneficial in preventing typhoidal relapses (Marmion) Moreover studies which provide for the simultaneous administration of living antigen and homologous killed antigen in suitable susceptible hosts are being pursued by various groups The ability of a killed antigen to provoke sufficient immunity before the incubation period of the active infection has transpired may be of practical importance

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weeks when customarily such tubes go into the discard But we reported that if one holds those tubes ten twelve fourteen or sixteen weeks one will not uncommonly find growth in them The bacilli thus recovered after prolonged culture grow quite normally on transplant and produce disease and death of animals with regularity Recently Hobby Auerbach and their associates have made an excellent study of this question

The bacilli are recoverable very readily by satisfactory techniques The data which we are to present derived from 109 specimens which came from fifty patients These lesions one thinks of very loosely as representing closed or open cavities By open one means a cavity having a bronchial communication The term closed cavity implies that the wall—the structure—is that of a cavity but there is no bronchial communication the walls of the bronchus having been fused as a result of the disease The material in these cavities is ordinary cavernous caseous material and detritus

Occasionally one encounters the so-called ghost cavities which represent open healing These structures retain the character of cavities except that their entire lining is made up of thin fibrous tissue Specific data on the results of these studies which will interest you are expressed graphically in the accompanying figure

RESECTED LUNG TISSUE STUDY

Fig 1

THE DEATH AND RESURRECTION OF THE TUBERCLE BACILLUS

By HENRY S. WILLIS, M.D. AND (*by invitation*) H. M. VANDIVIERE, IRENE MELVIN AND W. W. LORING

CHAPEL HILL, NORTH CAROLINA

This term, death and resurrection, is used advisedly. We do not propose to indulge in any philosophical discussion but it does seem to us of interest and possible importance that tubercle bacilli recovered from tissues may survive and grow only after they are incubated for a long period in contrast to the usual six to eight weeks as has been conventionally established.

The phenomenon of visible but apparently nonviable bacilli is before us now. This phenomenon has been noted a few times more or less in passing but apparently there has been no recognition of its significance until recently. Stanley Griffith in 1929 in England, observed this. Sweaney in this country and recently Beck and Yegian have reported some work on the recovery of bacilli which appeared in the tissues but did not grow in culture.

All of us have pondered how or by what mechanism the body kill off bacilli. We know large numbers of them must be destroyed but some how in this disease a few always remain, quite reminiscent of what Dr. Woodward was just commenting on for the etiological factors in malaria and numerous other diseases. This points to a near but not complete natural immunity of which we know nothing as yet.

In both clinical and experimental tuberculosis, as everyone knows, the bacilli become buried deeply in the tissues where they remain for long periods of time, even many years after all signs of clinical infection have long since disappeared.

We have not had the available techniques for very long for studying this matter and for recovering embedded bacilli from tissues and culturing them. In fact such techniques have been at hand only since the advent of chemotherapy for this disease. Now it is quite easy for the surgeon to lift out a piece of lung or a whole lung with virtual impunity and to turn the lung over for extensive bacteriological search.

As a result of these matters we were able to report an incidental observation before this society three years ago that one may demonstrate tubercle bacilli in the secretion or the materials from a cavity or from other tissues removed by operation and plant such material on culture medium only to find no growth at the end of the conventional period of six or eight

RESECTED LUNG TISSUE STUDY

TUBERCLES
(CM
23 P TIE S

39 SPECIMENS
100%

4 SPEC ME S
10%

TOTAL

O POSITIVE AT
8 WEEKS

NO POSITIVE ON
EXTENDED NCUB

GRANULOMAS
(TUBERCULOM S)
6 ATR TS

8 SPECME S
100%

1 SPECIMEN
2%

TOT L

NO PO IT E T
8 WEEKS

NO POS TIVE D
EXTENDED NCUB

G OST
(CYSTIC) CAV TES
6 PAT EN S

8 SPECME S
100%

NONE

TOTAL

NO POS T VE AT
8 WEE S

O POS TI E ON
EXTENDED INCUB

LEGEND: X SMEAR RESULT
MC PATIENT E EQUIV SPECIMENS
I/II=MOS SM/MOS INH.

DURATION OF EXTENDED CUB
NECESSARY FOR GROWTH

(O) NO SENSITIVITIES AV
(S) SENSITIVE
(R) RESISTANT

FIG. 4

This chart shown as figure 1 represents the data on some of these studies Twenty four patients provided 26 open cavities Twenty two or 85 per cent of the twenty six yielded tubercle bacilli which grew normally at eight weeks One required extended incubation for its appearance on the tube

With the sixteen so called closed cavities, no growth occurred at eight weeks of incubation, but 44 per cent of them showed growth over pro longed incubation one at two months one at three two at four one at six one at eight and one at ten months after culturing that i those cul tures were retained in the incubator for a maximum of ten months after the planting of material recovered from the tissues and only at these periods did they begin to grow The growth thus was slow in starting but when bacilli were recovered from it they looked perfectly normal and when transferred to other culture media they grew in normal fashion When put into animals they produced disease and death

In a number of these specimens the tissue came from tubercles of one centimeter in diameter or less There were 39 specimens from 23 patients and bacilli seldom grew as you see

Figure 2 reveals the results from eight specimens of so called tuberculoma or granulomatous tissue Culture from one grew in the conventional period none grew at extended periods From the so called cystic or ghost cavity eight specimens none grew

A little speculation may be in order here

A summary of the data presented in figure 3 indicates particularly in the column on the right the status of these bacilli which are recovered from the various types of lesion or cavity From the open cavity 85 per cent of them showed bacilli on smear and 81 per cent of these in the normal culture period 4 per cent (1 specimen) in protracted culture Interesting results fell out Of these cultures from open cavities 70 per cent were found to be resistant to drugs with which the patient had been treated whereas of those from the closed cavities only 17 per cent of the cultures were resistant In the other closed areas only an occasional culture showed resistant bacilli

The bacilli have been shut away in tissues which may not be very ac cessible to the ordinary flow of secretions or body fluids They are shut away from the free oxygen so available in the respired air and circulation is poor in the lesions One does not know all of the reasons for this lack of growth but the bacilli are buried in this area away from the open cavity away from the re pired oxygen and 10 per cent of the specimens produce growth instead of 85 as we find in the open cavity

So the bacillus imbedded deep in the tissues apparently is not nearly as reachable by the drug or accessible to the drug as those are in the open

The fact that bacilli which we ordinarily regard as being dead become alive again and active is a matter of major interest which we wanted to bring today One can get specimens from closed lesions—closed cavities granulomas or tubercles and incubate them after neotetrazolium has been added and find that a certain few of the bacilli will develop engorgement of what we presume are mitochondria at least the growing portions of the bacilli Apparently those which take on the mitochondrial change or show capacity for metabolic activity in that circumstance are those which grow promptly when planted on culture One wonders why it is that most of them are killed off but still a few live

Edmond Long in talking about this phenomenon one day said perhaps these bacilli resemble John Brown's body they lie mouldering in their graves but their spirits go marching on

DISCUSSION

DR JAMES M FAULKNER (Boston) I wonder if Dr Willis has any information about the location of the so called dead organisms whether they are intracellular or extracellular

DR THOMAS McP BROWN (Washington D C) I think this is a very significant paper There is some evidence that various materials present in closed tuberculous cavities have anti tuberculous activity From the studies of DuBos one notes that substance such as lactic acid fatty acid and the proteolytic enzyme resulting from the tuberculous antigen antibody reaction have a suppressive effect on the tubercle bacillus My question would be whether or not in a situation where the cavity was open to the bronchus such materials would escape thus being unavailable to interfere with the growth of the tubercle bacilli and positive cultures under these circumstances would be more likely

My second question relates to the statement that after long term streptomycin and PAS therapy viable tubercle bacilli may be found but these organisms are incapable of multiplication and are presumed dead Has there been any evidence of growth of these organisms in the speaker's experience after 10 months incubation?

DR JOHN H SKAVLEM (Cincinnati) Could I ask Dr Willis whether he would rather leave an open healed cavity or a closed cavity?

DR HENRY M THOMAS JR (Baltimore) I cannot help thinking how interested Dr Edward Livingston Trudeau would have been in this paper He was a member the first year of this organization and an officer later on and for years as you know the only person in this country who could keep a tubercle bacillus growing at all

DR HENRY S WILLIS (Closing) Mr Chairman in response to Dr Faulkner's question as to location whether the bacilli are intracellular or extracellular I can only say this In preparations where we use tetrazoleum for a measure of viability bacilli may be found—either intracellularly or extracellularly—which have taken up the dye converted it to produce blue formazan or in the case of regular tetrazolium red formazan So I would suspect that the bacillus may be intracellular or extracellular

Dr Brown I believe asked about whether the proteolytic enzyme and lactic acid might likely have effect in that circumstance That is interesting and is a point which we have not cogitated much on but will do so He also asked about the sputum culture of patients under long term treatment who were positive on

Type L	Total Spe m	Pos t e Sm	Pos t e 8 week lt e	Pos t e O t led bat	Re t tt Drug m &/ r INH
Open cavity	(26) 100%	(2?) 8?%	(21) 8?%		(11) ?0% (en t tivitie not av on 5)
				(1) 4%	(0) 0%
Clo ed cavity	(16) 100%	(16) 100%	(0) 0%		(0) 0%
				(?) 44%	(1) 1 % (en t tivitie not av on 1)
Granuloma (tuberculoma) >1 cm	(8) 100%	(8) 100%	(1) 1?%		(0) 0%
				(0) 0%	
Tul ercle <1 cm	(39) 100%	(3) 95%	(?) 5%		(0) 0%
				(?) 5%	(0, 0%
Ghost (cystic) cavity	(8) 100%	(?) ?5%	(0) 0%		(0) 0%
				(0) 0%	
Lymph node	(6) 100%	(3) 50%	(1 17%		(1)
				(0) 0%	
			(?) 33%		(1) Enhanced by INH
Mucu plug	(6) 100%	(4) 66%			
				(1) 1 %	(1)
Total	(100) 100%	(9?) 84%	(27) %	(11) 10%	(15) 40% of total

Lymph node eroded into bronchus with good aeration

Fig. 3 Resected lung tissue study

cavity If one combines this with the fact that *metabolic activity of the bacilli in the closed lesions is apparently of a very low order (because they do not grow as just indicated) it causes one to suppose or to wonder whether in this low state of metabolic activity they are actually very susceptible to the effects of drugs*

RANDOM NOTES, ENTOMOLOGICAL AND CLIMATOLOGICAL

By JAMES J. WARING, M.D.

DENVER

In 1948 Sir Russel Brock in a valuable paper on "Recurrent and Chronic Spontaneous Pneumothorax" included in his list of the causes of this form of pneumothorax the somewhat surprising term "cuckoo spit." Since I was somewhat familiar with the frog hopper or spittle insects of the family *Cercopidae* and had often seen in New England and elsewhere the walnut sized masses of froth resembling spittle on the stems of grasses and weeds, I was intrigued with Sir Russel's use of the term. Since Americans, including myself, are generally much less well informed than Britishers on the wonders of the Natural World I ventured to think that this audience might be interested in some random field notes. I also wondered how many doctors at home or abroad seeing this term "cuckoo spit" in Sir Russel's list pursued it through the insect world. I hasten to add that my entomological knowledge is still abysmal. When Sir Russel thoracoscoped his patients with recurrent and chronic spontaneous pneumothorax he observed in four cases out of 71, on the moist lung surface clusters of air bubbles in tiny areas resembling the froth seen on plants in early summer and called "cuckoo spit." According to Brock these areas are caused by minute and multiple alveolar leakages of air into subpleural tissues. Brock postulated that in certain cases intrapleural leak might occur and thus produce chronic pneumothorax. We now leave the Medical World for a brief tour of the Insect World.

The frog hoppers or spittle insects belong to the sub family *Aphrophorinae* of the family *Cercopidae*. The species *Philaenus spumarius* and *P. lineatus* are said to be common in New England. The insect photographed by Van Riper is the *Clastoptera lanneahcollis*. The one illustrated in Webster's New International Dictionary, 2nd edition, is named *Ptyelus lineatus* which brings back shades of Vesalius (1514–1564) who described the pituitary body and gave it the formidable misconceived name *glandula pituitam cerebri excipiens* and taught that it secretes the mucus discharges of the nose. It was some time before Richard Lower of Cornwall (1631–1691) and

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Professor of Medicine, Emeritus, University of Colorado School of Medicine. President, Colorado Foundation for Research in Tuberculosis.

Some of the slides shown at the time this talk was given were taken from the splendid illustrations of Ross, Curney and Hermes. The kodachromes of the living insect and the egg case were made by Walker Van Riper, Curator of Spiders and Insects to the Denver Museum of Natural History.

in microscopy but not in culture Approximately 1 per cent of patients now under current therapy will yield bacilli which will be negative under conventional techniques but will be positive if they are kept sixteen to twenty weeks That indicates that we have been missing some so called positives by rapid discarding of cultures

Dr Skavlem asked about the open healed cavity I am always afraid to leave an open healed cavity in the chest because I would suppose it might be a seat later for various infections and the patient would get cystic disease as a chronic affection

However we are sending patients home now with these cavities wide open Bacilli are totally absent from the secretion the patients are without symptoms A few of them have been operated upon but for the most part they are home now for as long as two and one half years without signs of disease coming on as yet

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Fig. 1. Cuckoo spit. Photo by Walker Van Riper.

Schneider (1614–1680) showed that nasal mucus or pituita comes from glands in the nose and is not filtered from the brain through the cribriform plate of the ethmoid bone.

Our true spittle bug is a small brown, gray, green or clay yellow colored insect. In the autumn eggs are laid on the stems of grasses or weeds and are hatched in the spring. Female spittle bugs make a froth to cover their eggs and later the young nymphs also make a froth which surrounds them and is the "cuckoo spit" of this narrative. It was formerly thought that the



FIG. 2. Nymphs of frog hopper with "Cuckoo spit" removed. Photo by Walker Van Piper

spittle which surrounds the larva was excreted from the anus. One authority says the excreted fluid is clear and contains no bubbles but by a constant thrashing about of the tail end of its body the frog hopper brings in air which is whipped into foam readily because of its viscid quality. Edwin Way Teale is more specific. He says a kind of bicycle pump formed of overlapping plates beneath its abdomen provides a chamber into which air is repeatedly drawn and expelled and permits the insect to produce

bubbles in the sap which it has sucked from the plant This little mass of foam not only protects the young larva from the hot rays of the sun and perhaps from stray insect and bird enemies but provides needed moisture

As to the association of 'cuckoo' to this spittle my researches indicate only the ancient erroneous popular belief that the matter was spit out by the cuckoo bird Much of pleasant fancy is associated with the words compounded of cuckoo! Sir Thomas Browne says It is declared by many that cicades are bred out of Cuccou spittle or Woodseare And elsewhere I read If on a May morning you rub your eyes with Cuckoo spittle you may see the fairies And again I read that There is a kind of Cuckoo pint in New France that if you break a branch of it will afford you a pint of excellent water Shakespeare lists the cuckoo flowers among what he calls the idle weeds You may hear the voice of the cuckoo in Beethoven's lovely *Pastoral Symphony According to the musical member of my* family Beethoven's notes are D followed by A sharp

Much more could be said about the cuckoo bird and the derivations and associations attached to its name Everyone is familiar with its adulterous implications Some may not know that the coccyx or tail bone is derived from the Latin word *cuck* meaning to pass excrement and that for some reason the coccyx has been called in not too refined literature 'the whistle bone

Here endeth the random note on Cuckoo Spit!

Random Note No 2

In 1946 when this Association was meeting at Hershey, Pennsylvania I strolled one afternoon in the lovely rose garden on the hotel grounds Suddenly a large insect like a miniature helicopter flew leisurely past my head Identification was easy it was a praying mantis! Determined to have a close look I took off fortunately down hill and arrived at the very moment this strange insect lit at a convenient spot in a rose bush When my inspection became quite close the creature (about three inches long) astonishingly aware and resentful of my presence turned his head upon a swivel neck and without the slightest sign of fear gave me a dirty look! Now I thoroughly sympathize with the poor insects which freeze with terror when this carnivorous creature looks at them This not so wee not at all cow rin nor tim rous beastie created a minuscule panic in my breastie! I was reminded of the time I came within a few feet of a weasel in the grass on the side of a mountain The flat head of the mantis its fearlessness and menacing attitude reminded me of Mr Weasel From the gardener I got several egg cases of the mantis and brought them back to Denver I am indebted to Van Riper for some beautiful pictures of the egg case and the living insect My chance acquaintance was probably a female Chinese mantis The Carolina mantis is the best known native mantis of the Eastern

states According to Gurney it may be found from Pennsylvania across the Middle West to Colorado and South into Mexico Altogether 19 kinds of mantids are found in the United States most of them in the South The name *mantis* is derived from the Greek meaning a *prophet* or soothsayer In some parts of the United States they are called rear horses devil horses and mule killers terms descriptive of their attitudes and the popular belief in the South that they kill mules Its habit of holding up the front legs and standing without moving for many minutes has given rise to the common name the praying mantis and the scientific term of the European species *Mantis religiosa* The Arabs still say that when it prays it turns its face toward Mecca The French peasants call it the Prie dieu (Provencal lou Prego Dieu) A more realistic name would be the Preying mantis since it feeds entirely upon other insects and obviously prefers a high protein diet They can be reared in the home and fed by hand upon house flies grasshoppers meal worm larvae or in more select circles upon tiny bits of uncooked liver hamburger or frankfurter In 1907 the first American fossil mantis was found in the Florissant field of Colorado which has yielded more fossil insects than any other in the world The age is thought to be 30 to 40 million years ago in the Miocene period

I will conclude this Random Note with a quotation from Jean Henri Fabre on the love making of the terrible praying mantis Says Fabre 'If the poor lover is loved by his mistress as the giver of fertility she also loves him as the choicest of game During the day or at the latest on the morrow he is seized by his companion who first gnaws through the back of his neck according to use and wont and then methodically devours him mouthful by mouthful leaving only the wings Here we have no case of jealousy but simply a depraved taste

I had continues Fabre the curiosity to wonder how a second male would be received by a newly fecundated female The result of my inquiry was scandalous The mantis in only too many cases is never sated with embraces and conjugal feasts After a rest of variable duration whether the eggs have been laid or not a second male is welcomed and devoured like the first A third succeeds him does his duty and affords yet another meal A fourth suffers a like fate In the course of two weeks I have seen the same mantis treat seven husbands in this fashion She admitted all to her embraces and all paid for the nuptial ecstasy with their lives Here ends my Random Note and the quotation from Fabre on the love affairs of the Mantis For further detail I refer you to that distinguished naturalist

Random Note No 3

Last year in the discussion of Dr Walter Palmer s paper on Ulcerative Colitis our distinguished secretary Dr Marshall Fulton related the interesting story of a 60 year old woman with ulcerative colitis high fever rapid

bubbles in the sap which it has sucked from the plant This little mass of foam not only protects the young larva from the hot rays of the sun and perhaps from stray insect and bird enemies but provides needed moisture

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FIG 3 Pneumatosis cystoides intestinalis Infant Double ring shadows

The next slide shows the typical roentgenogram of the abdomen of an infant with pneumatosis This baby entered the Colorado General Hospital as a feeding problem doubtless based upon birth injury It is possible that forced feeding may have had something to do with developments At any rate about the 9th day in the hospital the baby developed a bloody diarrhea great abdominal distention and the cystic condition which you see in this x ray Treatment consisted in gastric suction The following morning the distention had greatly decreased The bloody diarrhea had ceased A barium enema revealed no obstruction of the bowel A week later an x ray of the abdomen was interpreted as showing almost complete disappearance of the gas cysts The baby left the hospital shortly thereafter improved Dietary deficiency, forced feeding either or both may have had something to do with the development of this strange disorder

pulse and a remarkably distended abdomen Under treatment with ACTH antibiotics transfusions and other supporting measures she made a dramatic recovery Three weeks later when ready to leave the hospital an x ray of her chest showed gas beneath the diaphragm on both sides[1]

In a curb stone talk with Dr Fulton later I suggested the remote possibility that this might have been a case of *pneumatosis cystoides intestinalis* a rare condition characterized by innumerable small gas containing cysts in various portions of the gastro intestinal tract Spontaneous pneumoperitoneum without other evidence of perforation of a viscus has been frequently described It should be noted also that this condition has been reported in association with atypical ulcerative colitis Characteristically in such instances there would be a sudden remission of symptoms and a restoration of x ray signs to normal within a few weeks

Since this pneumatosis this condition of abdominal gas cysts is quite rare I venture with the permission of my pediatrician colleagues at the Colorado General Hospital to report a case in a new born baby First however a brief general comment Koss in a most comprehensive article reviews 194 papers describing 255 cases of this disorder Apparently it may occur at any age and more frequently in males than females In 58 per cent of cases the development of cysts is associated with a more or less obstructive lesion of the pyloric area principally a peptic ulcer In some 15 per cent of cases in which no other lesion is demonstrated so called primary pneumatosis isolated involvement of the cecal area with sub mucosal location of the cysts is frequently found Koss suggests the possibility that further investigation of this group may reveal a portal of entry in the appendix In infants the cysts are most frequently located in the submucosal area in adults in the subserosal area Cysts may be found in the mesentery in the parietal peritoneal wall in the gastrohepatic ligament falciform ligament gall bladder diaphragmatic peritoneum and retro peritoneal lymph nodes The size of the cysts varies from a millimeter to several centimeters According to Steinnon (1951) the roentgenographic findings may be (1) typical reticular appearance of the abdomen produced by cysts containing gas (2) double ring shadow of the bowel (3) otherwise unexplained pneumoperitoneum (4) unusual accumulations of air in the vaginal wall retroperitoneal and perirenal tissues (5) separation of liver from right leaf of diaphragm (6) atypical ulcerative colitis

No very satisfactory explanation has been given for this condition However since it is frequently found in hogs I asked Dr C I Davis Pathologist to the United States Bureau of Animal Industry in Denver if he could bring me a specimen from the Denver stockyards He said he could and did the next day I show you a kodachrome slide of this piece of hog gut

THE GORDON WILSON LECTURE

Observations on Certain Viruses Causing Exanthematous Diseases in Man

By JOHN F. ENDERS, Ph.D.*

BOSTON

In this lecture I propose to review certain observations especially in respect to etiology which my associates and I have made on three exanthematous diseases. All these conditions are usually benign. Two of them among the minor plagues of mankind are old acquaintances; the third has only recently emerged as a clinical and epidemiologic entity.

Many in this audience will, I feel sure, wonder why anyone should spend much time in reinvestigating measles, chicken pox and a mild infection which, for lack of a happier epithet, we have so far referred to as "an unusual epidemic exanthem," when other conditions of a more serious or dramatic character remain to be explained and controlled. Our reasons for so doing are several. With little doubt the underlying emotional impetus lay in the challenge presented by the fact that in spite of many endeavors by workers in the past no satisfactory ways had been found to isolate and maintain the agents of measles and chicken pox in the laboratory. We were also impelled by motives of a more purely scientific character. Thus if it should prove possible to discover means whereby these viruses could be propagated at will, a systematic study of their properties might be carried out. The results would almost certainly serve to extend in a profitable manner that body of rapidly increasing knowledge which is now designated by the somewhat unlovely name of "virology." In turn the acquisition of such information might lead to the development of methods of diagnosis and control.

Exploration of the exanthematous disease that I have just mentioned has been accomplished almost entirely by my former associate Dr. Franklin Neva. It was undertaken opportunistically because this infection manifested itself in the form of a widespread epidemic in Massachusetts during the summer of 1951. Since the physicians were unable to classify it among any of the known rash diseases, it obviously became a matter of much interest to define, if possible, the responsible agent.

Because the tissue culture enabled us in a large part to accumulate the

* Chief, Research Division of Infectious Diseases, Children's Medical Center, Boston, Massachusetts; Professor of Bacteriology and Immunology at the Children's Hospital, Harvard Medical School.

Summary

In these random notes I have called attention to alveolar leakage as a possible cause of chronic and recurrent pneumothorax to Brock s use of the term cuckoo spit and its entomological associations to strange insects sometimes found in rose gardens at Annual Meetings of this Associa tion and finally to the characteristic x ray appearance of that comparatively rare and as yet inadequately explained disorder pneumatosis cystoides intestinorum hominis!

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new group of respiratory viruses first described by Rowe and his associates[4] as well as the so-called orphan human enteric viruses or ECHO viruses * representatives of which were first obtained in our laboratory[6, 7] and have been subsequently and extensively studied by Melnick[8] Sabin[9] and others rests in part upon the recognition of this fact

Just as the growth of virus may occur only in the presence of cells from a susceptible species so multiplication may take place only in a given type of cells such as fibroblasts or epithelial cell elements derived from that species Although in the earlier literature there are to be found a few examples of such cytotropism *in vitro* recent observations have stressed its importance in the selection of media for the cultivation of certain viruses

A third factor and perhaps the most decisive of all in formerly limiting the value of the tissue culture was the difficulty in avoiding contamination by various microorganisms Elaborate precautions had to be taken to prevent the entrance of bacteria which greatly restricted the number of cultures that could be prepared and maintained Moreover it was possible to introduce into the system for examination only materials which had been rendered free of bacteria by filtration—a procedure which no doubt often reduced any virus that might be present to a sub infectious level When antibiotics became available this situation was entirely changed At present not only can very large numbers of cultures be employed as routine but also specimens of feces or throat washings may be added with little chance that bacterial growth will follow

Of late other advances in technique have been made which increase enormously the usefulness of the method Most notable perhaps are the introduction of cultures of human malignant cells by Scherer Syverton and Gey[10] and the preparation of normal and malignant cell suspensions by prolonged treatment of the tissue with trypsin The procedure of trypsinization devised many years ago by Rous and his associates but almost forgotten until recently was reintroduced by Dulbecco and Vogt[11] in 1953 By its means material sufficient for practically unlimited numbers of cultures can be obtained the use of a plasma matrix avoided and a mass of cell growth developed in which the cytopathic changes induced by virus are admirably revealed

For two reasons I have run the risk of boring you with this most imperfect sketch of some of the recent technical advances in the art of tissue culture as applied to the cultivation of viruses In the first place I wanted to make it evident that the method has been developed to a point that renders it almost as indispensible and as versatile in both the theoretical

* It has very recently been proposed that viruses having these properties be designated provisionally as ECHO viruses (Enteric Cytopathogenic Human Orphan Virus)

data which I am about to review I shall by way of additional introductory matter comment briefly on this valuable method Although the procedure has been employed on occasion to the study of viruses by many investigators during a period of over forty years, its potentiality did not become fully apparent until quite recently Three circumstances at least may be cited to account for the relatively meagre harvest of results gathered in the past by means of the tissue culture

The first of these was the failure to distinguish constant and reliable criteria for the multiplication of the virus within the culture system itself analogous to the manifestations of the disease in experimental animals To determine, therefore whether or not virus had increased it was nearly always necessary to inject susceptible animals with material from the culture Accordingly for most purposes cultivation *in vitro* of the virus appeared to offer no advantages over direct animal inoculation

In this respect the shortcomings of the tissue culture have in many instances been overcome by demonstration of the fact that the majority of viruses so far examined produce as they multiply, degenerative changes in the cells These changes are often apparent within a few hours or a few days after the viral inoculum is introduced and frequently are sufficiently characteristic to permit a tentative identification of the virus under examination Such effects are now referred to as cytopathic changes or as 'cytopathogenic effects of the virus

Although cytopathic changes were noted earlier by various investigators especially by Ivanovics and Hyde[1] in 1932 and Huang in 1942 their full significance was not generally appreciated until 1950 when it was demonstrated[3] that the viruses of poliomyelitis were highly cytopathogenic in cultures of a variety of several human tissues Since that time results obtained with a large number of viruses and a variety of cells from various species show that exhibition of cytopathogenicity *in vitro* affords criteria of viral multiplication as reliable as the production of signs of infection in animals Moreover such criteria may be often more conveniently and accurately observed

A second circumstance responsible for the earlier unfruitfulness of the method lay I think in the lack of adequate appreciation of the fact that multiplication of certain viruses depends upon the presence of cells derived from susceptible animals Previously it was unclear whether or not the natural host virus susceptibility relationship was maintained in isolated cell systems Numerous workers therefore continued to employ tissues that were most easily procured in the laboratory such as those of the chick embryo or the rabbit s testicle in unsuccessful attempts to cultivate viruses like those of poliomyelitis or chicken pox which are characterized by a high degree of specificity both *in vivo* and *in vitro* The isolation of the

TABLE I

Summary of Principal Features in 16 Patients with Epidemic Exanthem

Feature	No. Patients	Data and Remarks
Age distribution		Age in Years
	2	2
	10	2–4
	3	6–8
	3	Over 20
Fever		Temperature F
	4	100 or less
	5	101–103
	3	104–105
	4	Present—no record
Exanthem		Degree
	4	Prominent
	7	Moderate
	5	Minimal
Mucous membrane lesions (oral)		Appearance
	3	Definite
	1	Doubtful—similar to herpangina
Other features		Enlargement of tonsillar, cervical or occipital nodes in one half
		Chills, headache, myalgia in adults with minimal exanthem

Summary from data published by Neva, Feemster and Gorbach

Pittsburgh in 1954 which was likewise investigated by Dr Neva[12] A careful study of a limited number of cases in households both in Boston and Pittsburgh revealed a high communicability and showed that both children and adults were attacked The incubation period was defined as ranging between 3 to 8 days In the majority of instances however symptoms appeared 4 to 5 days after exposure The disease was mild lasting only from 2 to 5 days Its manifestations were definitely influenced by age In children most of whom fell in the 2–8 year group a febrile period of one or two days was either followed by or associated with a pink maculopapular skin eruption over the face trunk and extremities which persisted for 2 or 3 days In figure 1 the appearance of the rash is illustrated Systemic signs and symptoms were usually minimal Occasionally moderate enlargement of the lymph glands of the head and neck were observed but this was by no means a constant feature In contrast the illness in adults was prominently distinguished by systemic manifestations such as chills and fever severe headache and muscle pains and aches In only one half of the older cases studied was a rash observed It was frequently minimal and occurred regularly after defervescence The principal manifestations in 16 of the Massachusetts cases are summarized in Table I Obviously the disease in children exhibits

and practical study of viruses as the agar plate and the broth culture in the field of bacteriology Secondly, I felt that it might serve as useful background for some enabling them to visualize more precisely the means by which the etiologic investigations were carried out which I mentioned at the outset and which I shall now describe

Infectious Exanthem

I shall begin with the unusual infectious exanthem As I have said we first became aware of this condition during the summer of 1951 A subsequent study of cases of this disease as reported by pediatricians to the Massachusetts Department of Health indicated that it was widespread throughout the state since about 2 000 probable cases were recorded in this manner [12] Another but smaller outbreak of the same illness occurred in



Fig 1 Epidemic exanthem Appearance of exanthem in a two year old patient fourth day of disease (Reproduced by permission of Jour Am Med Asso)

first seen next to the original explant (Figure 2). Thence they extend toward the periphery of the new outgrowth of spindle cells. The changes consist of rounding, nuclear pyknosis and eventually in disintegration of the entire cell. Epithelial cells which also emerge in these cultures remain normal in appearance as shown in Figure 3. Similarly in cultures of human renal epithelial cells no cytopathic changes have been observed. The predilection of this virus for fibroblastic elements thus affords a good illustration of the need for using cultures containing various cell types in attempting isolation of unknown viruses.

Virus neutralization tests in tissue cultures were carried out with certain of the agents that were isolated employing paired sera taken during the acute and convalescent phase of the disease. In this procedure dilutions of the serum to be tested are mixed with a definite number of tissue culture infective doses of the virus. Then each mixture is added to several cultures. If the serum contains antibody specific for the agent under test cytopathic changes do not appear. In nearly all cases the development of specific neutralizing antibodies was demonstrated in this manner during the course



Fig. 3. Absence of cytopathic changes in sheet of epithelial cell outgrowth (lower left) with destruction of fibroblasts (upper right) following inoculation of a roller tube tissue culture of human prepucial tissue with virus isolated from patient shown in Figure 1. Mag 150X. (Reproduced by permission of J. Immunol.)



FIG 2 Degeneration of fibroblastic outgrowth adjacent to original explant in a roller tube culture of human preputial tissue following inoculation of virus isolated from patient shown in Figure 1 Mag 130× (Reproduced by permission of Jour Immunol)

certain features similar to rubella roseola infantum and heat rash and differentially must be distinguished from these conditions

Feces throat washings and blood obtained during the acute stage of the illness were inoculated into cultures of various human tissues [14] From 24 of a total of 27 cases thus examined cytopathogenic agents all closely similar in their properties were recovered In the large majority these viruses were present in the feces However they have also been isolated from the throat of three patients and the blood of one Isolation from the blood of an agent similar in all respects to those derived from the feces represent of course a particularly reassuring part of the evidence for the conclusion that the etiologic agent has been identified

Introduced into cultures containing human fibroblasts these viruses produce their cytopathogenic effect only after a period of 5 to 7 days This is a longer *in vitro* incubation period than is characteristic of agents like poliomyelitis virus which may cause cell degeneration within less than 24 hours In the fibroblastic outgrowth which predominantly occurs in roller tube cultures of human preputial tissues the cytopathic changes are usually



Fig 4 Appearance of focal area of cellular degeneration [illegible] days after inoculation of roller tube culture of human prepucial tissue with varicella agent (H & E Stain) Mag 100× (Reproduced by permission of Proc Soc Exp Biol and Med)

tube cultures of human embryonic skin and muscle tissue or post natal prepucial tissue small foci consisting of abnormal cells appear scattered at random throughout the layer of normal fibroblastic outgrowth These cells are easily recognized by increased refractility rounding of outline and moderate increase in size As cultivation is continued the foci enlarge and eventually through confluence as well as the establishment of new areas of the same sort all or nearly all the cells become involved and finally disintegrate Epithelial elements that may be present are likewise attacked by the virus and in general behave in a similar manner In Figure 4 is shown in a stained preparation a portion of a focus of injured cells adjacent to the layer of normal unaffected cell outgrowth The extremely sharp boundary between the normal and involved area is noteworthy Examination under higher power revealed in many cells eosinophilic intranuclear inclusion bodies closely resembling those regularly found in the dermal lesions of the disease itself The appearance of cells containing such inclusions are shown in Figure 5

These very characteristic effects have been regularly produced with

TABLE II

Results of Serum Neutralization Tests on Sera of Patients with Epidemic Exanthem Disease from Whose Feces Virus was Isolated

Patient	Strain of Virus Used as Antigen	Neutralizing Titers of Patient's Serum	
		Acute phase serum	Convalescent phase serum
M W	L W	<2	32
	V F	<2	16
L D	V F	<2	16
H H	L W	<4	16
	V F	<2	8
V F	V F	<2	>16
J C	L W	<2	>16
	V F	<2	>32

After Neva and Enders (14)

Reciprocal of dilution of serum preventing development of cytopathic changes in cultures of human fibroblasts when mixed with 100 ID_{50} of virus (ID_{50} = amount of virus capable of exerting a cytopathogenic effect in one half the number of tissue culture into which it was introduced)

of the illness Cross neutralization tests using the sera of one patient and the virus from another indicated a close similarity or identity of these agents Using the same technique Dr Neva[11] has lately found that complete crossing occurs between viruses and sera from the Pittsburgh and Massachusetts epidemics

The cytopathogenic effects of the agents associated with this disease resemble those produced by certain types of Coxsackie viruses as well as those of the ECHO group From Coxsackie virus they are distinguished by their lack of virulence for suckling mice The possibility however still remains that they may eventually be classified among certain of the ECHO agents It would seem however that we are justified in drawing the tentative conclusion on the basis of available clinical epidemiologic and laboratory data that a hitherto unrecognized disease has been delineated which is caused by a viral agent exhibiting a specific antigenic structure and a characteristic cytotropism *in vitro*

Chicken Pox

The apparent successful isolation of the varicella virus in tissue culture by Dr Thomas H Weller[15] in our laboratory represents the termination of many previous attempts to propagate this agent Its behavior *in vitro* contrasts sharply with that of the exanthem viruses and indeed in one respect which I shall describe immediately with that of all others we know

Following the addition of fluid from the vesicles of chicken pox to roller

to reproduce in cell cultures changes characteristic of the dermal lesion *in vivo* evidence for an etiologic relationship of the agent to varicella has been gained from the results of serologic procedures using acute and convalescent phase sera Virus neutralization tests have shown the development of an antibody in patients recovering from chicken pox which is capable of reducing significantly the number of foci in tissue culture when mixed with virus[16] Application of the Coons fluorescent antibody technique to cells removed from infected cultures has likewise revealed the emergence of a specific antibody capable of combining with viral antigen within the cell[17] Coons method consists in applying the serum suspected to contain the antibody to fixed and dried tissue cells containing the antigen Excess serum is removed by washing The preparation is then treated with a fluorescent antibody solution specifically reacting with the gamma globulin of the serum under examination—in this case human gamma globulin The complex of antigen and antibody is rendered in this manner visible under the fluorescent microscope In the discussion of our work on measles a figure illustrating this effect is included (Figure 9)

From the lesions of cases of herpes zoster Dr Weller[15] has in the same manner isolated a number of agents which produce cytopathic change indistinguishable from those caused by the varicella virus as shown in Figure



FIG 6 Intranuclear inclusions in cell outgrowth of human embryonic skin muscle in roller tube culture 2 days after inoculation with herpes zoster agent (H & E stain) Mag 575X (Reproduced by permission of Proc Soc Exp Biol and Med)

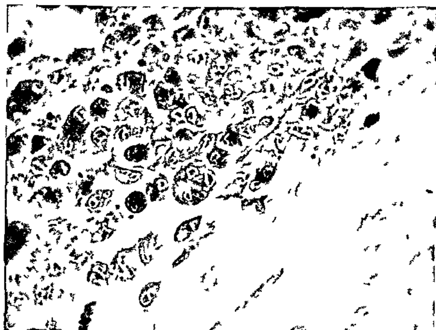


Fig 5 Edge of focal area of cellular degeneration Appearance on 6th day after inoculation of roller tube culture of human embryonic skin muscle tissue with another strain of varicella agent Note intranuclear inclusion and multinuclear giant cell (H & E stain) Mag 550× (Reproduced by permission of Proc Soc Exp Biol and Med)

vesicle fluids from a considerable number of typical cases of chicken pox A few representative strains of the virus have been maintained through many serial passages in tissue cultures over a period of three years and have continued to reproduce the same cytopathogenic effects

A unique phenomenon was revealed when these passages were first inaugurated It proved essential to include in the inoculum for passage a few infected cells This finding indicated that the agent at least in its infective form was not released into the culture medium as is the case with others which have been studied in tissue culture Even more surprising was the failure to separate the virus from the cells by a variety of rigorous procedures such as freezing and thawing and grinding with an abrasive We have here then a typical animal virus which under these conditions cannot be shown to exhibit infective properties when disassociated from the cell in which it multiplies The phenomenon is of interest from several points of view but in particular I think because of its possible bearing on the problem of viruses as incitants of the malignant state

In addition to its constant association with the disease and its capacity

Measles

Over fifteen years ago my associates at that time and I spent months in attempting to find ways of propagating the virus of measles in monkeys chick embryos chick embryo tissue cultures and even in cultures consisting of human placental tissue which unfortunately did not grow well On the whole we were unsuccessful although we did in accordance with the observations of previous workers note a scanty rash in an occasional monkey following inoculation with blood or throat washings from patients with the disease After we had shown that poliomyelitis could be cultivated in a variety of human tissues the urge to try the same system with measles virus became irresistible since in spite of intervening reports of its cultivation none had been generally confirmed Accordingly with Dr Thomas Peebles we introduced into roller tube cultures of human kidney tissue blood or throat washings taken from typical cases during the first 24 hours of the rash After a week or longer we found to our delight changes of a peculiar sort [15] As seen under low power these consisted of circumscribed areas in the cell outgrowth containing nuclei and cytoplasm but in which the cell boundaries had entirely disappeared Upon continued incubation

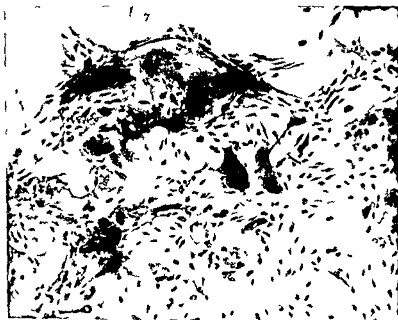


FIG 7 Appearance of cytopathic change in human renal cell 20 days following introduction of measles virus into a roller tube culture Note syncytial or giant cell formation (Fixed in formalin H & E stain) Mag approx 100×

TABLE III

Results of Exposing Tissue Culture Cells Infected with the Viruses of Varicella Herpes Zoster and Herpes Simplex to Sera from Patients with These Diseases and Subsequently to Fluorescent Anti Human Gamma Globulin Rabbit Serum (Coons Technique)

Source of Serum	Day of Illness Serum Obtained	Results: Cells Infected with Virus of					
		Varicella			Herpes zoster		Herpes simplex
		M E	W I	Pat	Bl	Sto	Rod
Varicella							
Case 1	3	0	0	±	+	0	±
	9	4+	4+	4+	4+	4+	+
Case 2	1	±	0	0	0	0	+
	[illegible]	4+	4+	4+	4+	4+	+
Herpes zoster							
Case 1	[illegible]	0	ND	ND	0	0	±
	51	3+	ND	ND	2+	+	±
Case 2	4	±	ND	ND	0	0	4+
	2[illegible]	3+	ND	ND	4+	4+	4+
Herpes simplex							
Case 1	A†	ND	ND	±	ND	ND	4+
	B	ND	ND	±	ND	ND	4+
Case	A	0	ND	ND	0	0	2+
	B	±	ND	ND	0	0	3+

Data from Weller and Coons

* Denotes Strain of virus employed

† Sera from cases of recurrent herpes simplex taken at varying intervals not related to appearance of typical lesions

6 Acute and convalescent phase sera from cases of varicella and herpes zoster and those obtained at various times from cases of recurrent herpes simplex were applied to tissue cells infected with the respective viruses in a variety of combinations as shown in Table III and examined by means of the Coons technique It is clear that the varicella and zoster sera exhibited marked cross reaction with sera taken during the convalescent phase of each disease while the sera from patients with herpes simplex failed to react with the viruses of zoster or varicella Results of complement fixation tests[16] using antigen prepared in tissue cultures which I shall not present in detail have likewise afforded additional evidence for the close antigenic relationship or identity between these two viruses Experiments are also in progress in which the capacity of convalescent sera to cross neutralize the cytopathogenic effects of the respective agents is being tested If the expected results are obtained it may be affirmed with much confidence that these two viruses are one and the same Absolute proof of course can be obtained only by inoculation of man Such experiments however are not contemplated at the present time

Strains exhibiting identical properties have been isolated from the blood of eight patients with typical measles. Some of these were isolated in 1954 and others in 1955. One other strain was obtained from the lung tissue of a fatal case.

Viral neutralizing antibodies capable of preventing cytopathic changes have been shown to develop regularly and promptly in nearly all cases of measles that we have examined. Examples of the titers obtained are given in Table IV. In the last instance it will be noted, the titer had probably reached its maximum at the time the first blood was withdrawn.

An antigen appears in tissue cultures which fixes complement with convalescent sera but either not at all with acute phase sera or if so only to a lower titer. The results of complement fixation tests on the paired sera of 25 cases are summarized in Table V. It is evident that an increase of four times or more, which is regarded as significant, was recorded in 22 instances.

In the sera of persons giving a positive history of measles this comple

TABLE IV

Results of Virus Neutralization Tests in Cultures of Human Kidney Tissue on Sera from Patients with Measles

Patient	Serum	
	Acute Phase*	Convalescent Phase†
I	<4‡	128
II	<4	128
III	>64	128

* Acute phase sera obtained from about 24–96 hours after appearance of exanthem.

† Convalescent sera obtained about 14 days after appearance of exanthem.

‡ Reciprocal of serum dilution preventing typical cytopathic change when mixed with 100 ID tissue culture doses of virus.

TABLE V

Summary of Results of Complement Fixation Tests on Acute and Convalescent Phase Sera of Patients with Measles

Total Cases	Number with CF Antibody Increased during Period Studied	
	4× or more	2× [illegible]
25	22 †	3

* CF Tests carried out according to method of Fulton and Dumbell as modified by Svedmyr, Enders and Holloway.[3] Undiluted nutrient fluid removed from tissue cultures infected with measles virus was employed as antigen.

† An increase of 4× is considered significant. The mean increase in the 22 patients was 31×.

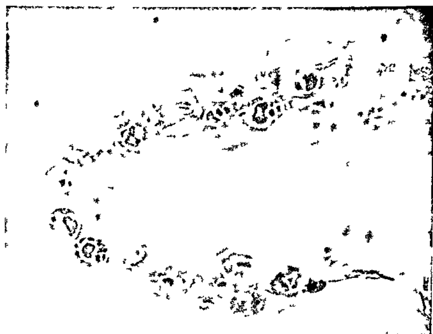


FIG 8 Syncytium or giant cell in outgrowth from human kidney tissue in a roller tube culture 18 days after inoculation of measles virus from the 4th serial tissue culture passage (Carnoy fixative H & E stain) Mag approx 800X

the cytoplasmic portion became increasingly vacuolated until it presented a torn or foamy appearance In fixed and stained preparations these areas were seen to represent syncytia or large giant cells which contained 40 or more nuclei Within most of the nuclei typical eosinophilic inclusion bodies were present The process proceeds in a leisurely manner to involve ultimately the whole layer of newly grown cells These interesting cytopathic changes are illustrated in the next figures (7 8) They are however not exclusively characteristic of the measles agent for it has been shown by Rustigian[19] that viruses latent in the kidney of rhesus monkeys may multiply in tissue cultures and produce very similar effects when these are observed in the fresh state So far however in our experience inclusion bodies in the nuclei of the syncytial formations have not been observed after inoculation of tissue cultures with Rustigian s monkey viruses In stained preparations therefore they have been easily differentiated from the measles agent

As I have just implied we believe that the virus which produces the effects in human renal cells we have described represents the etiologic agent of measles The evidence for this belief I shall in conclusion very rapidly summarize

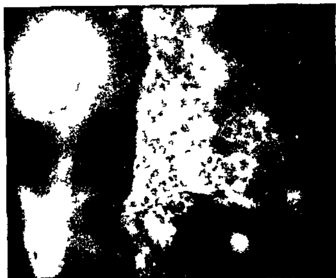


Fig 9 Appearance of syncytium from a roller tube culture of human kidney tissue 7 days after inoculated with measles virus (Edmonston strain 1[illegible]th tissue culture passage) treated with convalescent phase measles serum followed by fluorescent anti human gamma globulin rabbit serum Note that the fluorescent material is largely distributed between the nuclei The large very bright oval body is a bubble Mag 100×

Finally in cynomolgus monkeys a disease which in all essential respects closely resembles measles in man has followed inoculation of virus from the 23rd serial tissue culture passage of the virus In Figure 10 the data obtained in one animal are presented as an example The virus was introduced by both the intranasal and intravenous routes Thereafter no virus was recovered from the blood until the fifth day when it appeared and persisted until the 14th day From the 11th to the 15th day a rash was observed on the face trunk and extremities which closely resembled the exanthem seen in man Within a day or two after the disappearance of the rash and within four days after the cessation of viremia complement fixing antibody appeared in the blood which reached maximum titer within a few days The concentration of this antibody declined rather rapidly during the ensuing weeks

All these phenomena have not been seen in every monkey injected with the virus In some the rash has been absent or minimal although viremia has occurred In one animal neither rash nor viremia were noted In every case however antibody has developed So far we have failed to cultivate the virus in chick embryos or chick embryonic tissue cultures We are

TABLE VI

Summary of Results of Complement Fixation Tests on Sera of Persons with Positive or Negative Histories of Measles

History of Measles	Number of Persons Studied	Number Yielding Sera with CF Antibody Titer of*	
		4 or lower	8 or higher
Positive	17	3	14
Negative	13	13	0

* Reciprocal of serum dilution fixing 2 units of complement in the presence of nutrient medium from cultures of human kidney cells infected with measles virus

ment fixing antibody has usually been found, whereas in those with a negative history it has seldom been present In Table VI the findings in 30 individuals are recorded Additional data not included in the table are in general confirmatory A few deviations however, have been observed from the expected correlation In view of the difficulty of the accurate diagnosis of measles in all instances such discrepancies perhaps are not surprising

Antibody reacting with the virus has also been shown to appear in convalescent phase sera which can be demonstrated by means of the Coons technique [1] The appearance of the characteristic giant cells after application of the serum and subsequent treatment with fluorescent anti globulin antibody is illustrated in Figure 9 * Acute phase sera in general do not produce this effect The prominence of the fluorescent antigen antibody complex in the cytoplasm was unexpected in view of the fact that the intranuclear inclusion body represents the striking feature in cells stained by the ordinary method **

More indirectly the finding of high titers of both neutralizing and complement fixing antibodies which we have found in specimens of human gamma globulin supports the thesis that the agent is the cause of measles In view of the marked prophylactic effect of this material high concentrations of antibody for the virus of measles would be expected

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The experiments employing the fluorescent antibody technique were carried out in collaboration with Dr Albert Coons and Dr Barbara Watson of the Department of Bacteriology and Immunology of the Harvard Medical School and Dr Gisela Ruckle now of the Department of Preventive Medicine University of Pittsburgh Medical School

Cohen and her collaborators (92) have recently isolated viruses from cases of measles which conform in general in their properties with those of our agents Antibody developing in human convalescent measles sera was demonstrated by the Coons technique using cultures of infected monkey renal cells In certain instances considerable quantities *of fluorescent material were revealed within the nuclei*

inclined therefore to believe that this agent does not multiply under these conditions as reported by previous investigators In the renal cells of monkeys however multiplication has been shown to take place accompanied by cytopathic changes

In conclusion I would point out that if we are correct in thinking we are in possession of the etiologic agent of measles we have now the means of directly assaying the protective antibody in human globulin Furthermore the possession of the virus in a form that can be manipulated in the laboratory may lead eventually to the development of a practical way of inducing active immunity

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MEASLES IN A CYNOMOLGUS MONKEY

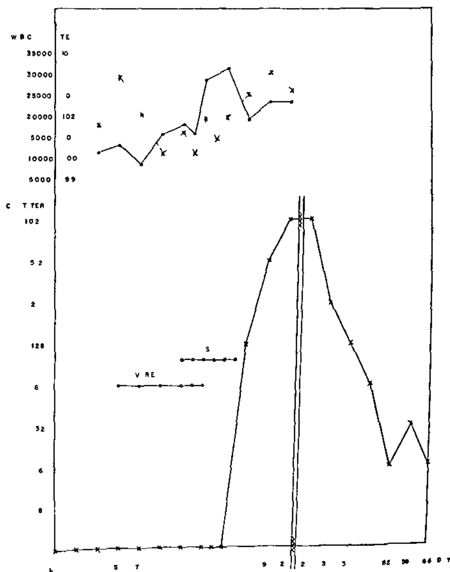


FIG 10 Data obtained following inoculation of a Cynomolgus monkey with measles viru (Edmonston strain 3rd passage in human kidney tissue culture) Undiluted ti ue culture 0 75 ml given intravenou ly and 0 25 ml intranasally WBC X - - - -X temp —— titer comp fix antibody X——X

SUCCESSFUL HOMOTRANSPLANTATION OF THE KIDNEY IN AN IDENTICAL TWIN

By JOHN P. MERRILL, M.D. AND (*by invitation*) J. HARTWELL HARRISON, M.D., JOSEPH E. MURRAY, M.D., AND WARREN R. GUILD, M.D.

BOSTON

Homotransplantation of the kidney, by which we mean the grafting of the kidney from one individual to another of the same species, has not to date been successfully accomplished with the exceptions to be mentioned. In spite of a vast amount of work in the animal laboratory, kidney transplantation in dogs has been uniformly unsuccessful. When a kidney is transplanted from one dog to another the course of the graft is similar in almost every case, regardless of the efforts made to modify it. Following transplantation, the kidney may secrete urine for periods varying from four to twelve days and then characteristically hematuria ensues, formation of urine ceases and the homograft no longer functions. When one examines such a kidney histologically, the picture is strikingly similar. Infiltration of the tissue by round cells is characteristic. There are scattered thromboses of the smaller arterioles with multiple small infarcts and edema.

In human homotransplants the story is much the same. As you might have guessed, the first attempt at transplantation of human kidney was made in 1936 by the Russians.[1] This, however, was not successful and the Soviet scientists then went on to attempt the invention of the steamboat, telephone and airplane. In our own country other sporadic attempts at human homotransplantation of the kidney were likewise unsuccessful. Last year Dr. David Hume, Dr. Ben Miller, Dr. George Thorn and I reported nine cases of transplantation of the human kidney. Of these nine, four developed significant renal function, and of these four, the function in two was of definite clinical importance. In one of these two cases, kidney function lasted for five and one half months following transplantation and enabled the patient, who had been admitted in severe uremia, to be discharged from the hospital, to travel and to lead a reasonably comfortable existence. In all but one of these cases the kidney was transplanted into the thigh where by the previous raising of a pedicle flap a pocket was provided for the transplanted organ. The renal artery was anastomosed with the profunda femoris in an end-to-end anastomosis, and the renal vein to the common femoral vein with an end-to-side anastomosis. The ureter was brought out through a skin ureterostomy, and the urine from this skin ureterostomy

From the Departments of Medicine and Surgery, Peter Bent Brigham Hospital, Boston, Massachusetts.

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the other questions posed above Richard H a 24 year old man with chronic glomerulonephritis was transferred to the Peter Bent Brigham Hospital following unsuccessful attempts in an outside institution to maintain him with conservative therapy In the week prior to admission he had had several convulsions and because of constant nausea and vomiting had been maintained entirely on parenteral therapy Shortly before admission he had become combative and overtly psychotic Dialysis with the artificial kidney resulted in good clinical improvement and he was able to leave the hospital three weeks after admission It had previously been suggested by Dr David Miller of the transferring hospital that because the patient had a twin brother renal transplantation might be possible We knew that if this twin was a monozygotic (identical) twin that there was real reason for considering this possibility We knew for instance that skin grafts had been made between identical twins and had taken permanently [4] Furthermore in 1950 the successful grafting of skin between identical twins was used by an English Court of Law to establish the identity of a twin who had been separated from his brother at birth [5] Therefore it seemed probable that skin grafts would take successfully between these twins if they were identical There was however no precedent for kidney homografts We knew though that skin and kidney transplants in animals showed the same type of histologic rejection response when the grafts failed We knew also that there appeared to be a *common* antigen in these tissues since skin transplanted from one animal to another would accelerate the rejection of a kidney transplanted at a later date It therefore seemed likely if the twins were indeed identical that a transplanted kidney might survive much as transplanted skin The next step was to establish beyond reasonable doubt that the twins were identical Although their parents were dead and the physician who had delivered them had died some years before it was possible to determine that there was a common placenta at birth With the help of the Blood Grouping Laboratory at Children s Hospital we were able to ascertain that the twins had identical antigens for 26 blood sub groups A geneticist who was good enough to help performed various taste tests studied the irises and the configuration of the ears among other factors and opined that the chances were 98 % that the twins were identical It was felt however that the best test of identity was the practical one i e the success of skin grafts transplanted between the two brothers This was done and the patient discharged from the hospital During this interval his blood pressure rose precipitously and he developed all the stigmata of the malignant hypertensive syndrome He was readmitted in severe distress with retinal hemorrhages and exudates marked cardiomegaly and both peripheral and pulmonary edema On December 17 31 days after the skin grafts had been made the transplant margins were biopsied and found to

collected by means of a colostomy cup attachment Eventually in all these cases the homograft ceased functioning Presumably failure was due to the same antigen antibody response which results in the ultimate rejection of all homografts with the possible exception of cornea However in this series there did seem to be some difference from the animal experiments The microscopic picture was not quite the same and the duration of function was of course much longer It seemed possible that since we had transplanted a sick kidney into a sick donor that this might in some way have modified the immune response Since many of these kidneys came from chronic cardiacs shortly after death and were transplanted into severely uremic patients it seemed possible that either the transplanted tissue or the host or both might be incapable of the violent rejection response which characterizes the transplantation of healthy tissue into a healthy host For this reason it seemed worth pursuing further the problem of transplantation of the kidney in the human

From the foregoing however it appeared that there were certain technical difficulties to be eliminated In the first place it was essential that the donor and the recipient have the same blood type It was necessary also that if possible we ascertain beforehand that the donor have a kidney which was free of disease Certain preliminary evidence made it seem important that the donor be pre treated in such a way as to further prevent the so called immune response Therefore the use of elective donors rather than cadavers would be important Secondly it seemed desirable to place the kidney intra abdominally rather than in the thigh In the majority of the previously described cases infection played a significant role in destruction of the kidney This might be avoided if we could obviate the use of the skin ureterostomy Thirdly we had to know whether the normal kidney might regain normal function after a period of anoxia such as would be necessary during transplantation Finally since the blood supply to the first third of the ureter is derived from the kidney itself one might be assured of good supply to the ureter and also avoid the possibility of uretero ureteral anastomosis with the consequent danger of stricture if the first third of the ureter were implanted directly into the bladder We were however somewhat concerned about this last point since this would necessitate placing the transplant in the pelvis and anastomosing it to the pelvic vessel We knew from previous dog experiments[3] that placing a dog s own kidney in an abnormal position in the same animal might result in poor kidney function However Dr Joseph Murray in a series of experiments transplanted a dog s kidney into the pelvis and ascertained after more than a year with a single kidney thus transplanted that the animals maintained normal renal function and good health

In the fall of 1954 we were afforded an unusual opportunity to answer

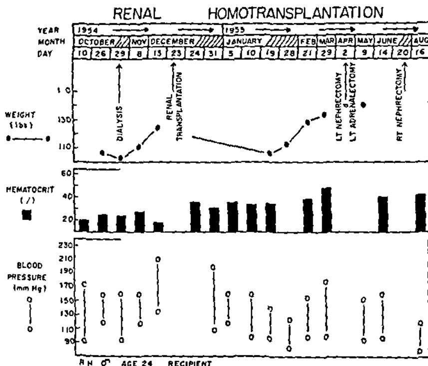


FIG II The increase in weight between the time of dialysis is due to the accumulation of edema fluid The subsequent increase in weight after transplantation represents healthy body tissue Note the striking drop in blood pressure following the grafting of a third kidney while both diseased kidneys were still in place Two months after operation blood pressure tends to rise again to drop following left nephrectomy rise slightly again and then drop to normal values following the removal of the second diseased kidney The rise in hematocrit to normal values is consistent with the general chemical and clinical improvement shown in both Figure I and Figure II

stars Following discharge from the hospital however the blood pressure rose gradually and the patient s urine continued to show two to four granular casts and six to ten white blood cells per high power field Because of the possibility of infecting the transplant from the two diseased organs and because of suggestive evidence that the presence of the two abnormal kidneys might result in reappearance of hypertension the left and then the right kidney were removed in separate operations without event Following this the urine became free of cells and casts and the blood pressure returned to normal At the present time the patient is well active and free of all demonstrable disease except that he continues to excrete three to four grams of protein per 24 hours in his urine

What conclusions may we draw from this interesting sequence of events?

show no evidence of the rejection response Six days later on December 23rd a kidney was removed from Ronald the healthy twin, and transplanted into the right pelvis of Richard The renal artery was anastomosed to the hypogastric artery and the renal vein to the common iliac vein The ureter was placed *in the bladder and a polyvinyl catheter placed therein* leading externally through a cystotomy The total period of anoxia of the *homograft was one hour and twenty minutes The postoperative course of* the donor was uneventful

Immediately after the clamps were released on the transplanted kidney it became pink and shortly thereafter urine was seen issuing from the plastic catheter The urine volume increased and renal function improved daily Figures I and II show the striking improvement during the postoperative course Of particular importance is the fact that following operation the blood pressure decreased to normal values and the cardiomegaly and edema disappeared The eye grounds became normal except for a few old

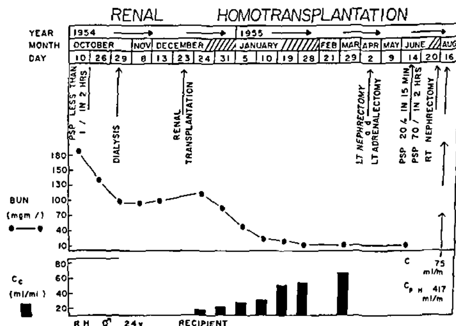


FIG I This figure demonstrates graphically the fall in blood urea nitrogen from 190 mg per cent at the time of transplantation to normal values where it has been maintained since operation Eight months after operation PSP excretion is within normal limits Following the removal of both kidneys the filtration rate of the transplanted kidney as measured by the clearance of inulin has shown some compensatory increase and *the renal plasma flow* even more of the compensatory increase of the calculated value for one kidney The clearance of creatinine plotted in solid bars at the bottom of the graph shows a progressive increase to values consistent with the inulin clearance

It dropped somewhat before you took out the patient's diseased kidneys but did not come down to normal, is that right?

DR JAMES J WARING (Denver) I would like to ask Dr Merrill what work Alexis Carrel did on the transplanting of kidneys. It seems to me that when I was at Hopkins in 1905 Carrel showed some dogs at that time in which he had done kidney transplantations as well as other vascular surgery.

DR THORNTON SCOTT (Lexington) I wonder if Dr Merrill has his patient on continuous penicillin prophylaxis against streptococcal infection because, as Dr Wood points out, identical twins are susceptible to identical diseases. In view of the role of the streptococcus in inducing glomerular nephritis one suspects that this patient would still be inordinately susceptible to it.

DR JOHN P MERRILL (Closing) In answer to Dr Wood's question the fact that one identical twin has hypertension makes the other much more susceptible.

But, interestingly enough, the only good series on nephritis has been run by Dr Addis. He had four pairs of identical twins, one of whom had glomerular nephritis and the other did not. So we feel a little happy about that, though, of course, the possibility disturbed us immensely.

The blood pressure dropped very dramatically within three or four days after operation when the third kidney and both the other kidneys were in place.

For four or five months we followed this boy quite carefully in the outpatient department, and what we saw was what one would see in following a patient who was susceptible to hypertension. He would come in, and his first visit blood pressure would be perhaps 135/85, then would drop to 120/80 if we rested him.

A month later, however, his initial pressure was 150/95 and would drop to 140/90.

Finally, when we got an initial pressure of 160/100 we decided that this perhaps was something more than lability of his vasomotor system, and we took out both his own kidneys.

But the important fact is that all his vascular disease did disappear while all three kidneys were in place, and, of course, the blood pressure dropped remarkably.

Dr Carrel did do a number of renal homografts. He took the aorta with both renal arteries and kidneys, and transplanted them. He did publish some work which indicated that the grafts had survived for long periods of time. However, the records were not available to us or others, and nobody since that time has been able to duplicate Dr Carrel's work.

With regard to prophylaxis, we obviously were very concerned about this. This boy is on penicillin prophylaxis (that is, oral penicillin), and we are extremely cautious about this.

At the present time, however, while he does have some proteinuria, he has no casts and no cells in his urine. The proteinuria, I think, might well be explained by the abnormal position of the kidney, because in dogs when the kidney is transplanted (in autografts, that is), if there is discrepancy between the *renal vein and the vein* with which it is anastomosed, the transplant does show some proteinuria. But a year and a half after operation in these kidneys our biopsies have not shown any renal lesion. *So we hope, or have some reason to believe, that this proteinuria is not due to* glomerular involvement but simply to the vascular problem involved in surgical procedure.

First and not least in importance that it was an effective therapeutic approach to Richard's particular difficulty Secondly that homotransplantation of the kidney in man is at least a technically feasible procedure Such a kidney can survive one and one half hours of anoxia and attain near normal renal function Important also is the fact that its abnormal position does not prevent attainment of this good function The observations on the remission of the hypertensive syndrome are perhaps of equal importance as they pertain to the etiology of renal hypertension in man Recent evidence suggests that the role of the normal kidney may be to metabolize or to excrete some pressor substance causing hypertension In this view renal hypertension may be due entirely or in part to something the kidney fails to excrete or metabolize rather than something it elaborates The fact that hypertension and hypertensive vascular disease disappeared in this patient when a normal kidney was transplanted even though the two abnormal kidneys remained in situ lends credence to this view The demonstration that a normal kidney can be successfully transplanted from one identical twin to another perhaps brings us no nearer to answering the fundamental problem of the immune response causing rejection than do previous efforts It does however allow us to proceed with the further investigation of this problem in animals with full confidence that its application to man has been reasonably established

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DISCUSSION

Dr Francis C Wood (Philadelphia) This of course interests me greatly I wonder if you have been in touch with Doctor Kallman of Columbia who has made a very extensive study of identical twins

I was wondering if he might know whether nephritis was apt to occur in both of two identical twins

Would you once more say something I did not see on your slide as to exactly what happened to the amount of urine excretion and how the blood pressure behaved

but from it one gets the impression that it is easier to find an excess of circulating *RPS* in shock hemorrhage heart failure and other conditions characterized by low blood pressure than it is in the hypertensive state In addition to raising blood pressure *RPS* increases the renal filtration fraction and maintains renal arterio-venous oxygen difference through a wide range of renal blood flow Teleology is a dangerous word but the evidence justifies the conclusion that the renal tubule participates in a homeostatic response to circulatory failure by liberating a substance which bolsters arterial pressure maintains glomerular filtration in the face of diminishing renal blood flow and adjusts the appetite of the kidney for oxygen to the available supply

The reasons why a potentially useful reaction like this occasionally persists and becomes a menace in its own right are presumably related to extra renal mechanisms since removal of the offending kidney has such an unpredictable effect upon blood pressure Improved diagnostic criteria particularly the introduction of renal arteriography have somewhat increased the percentage of good results from nephrectomy and all of us feel indebted to John Eager Howard for his contributions to this field [1] Even so less than half of the hypertensive patients who had a kidney removed for unilateral disease at the Mayo Clinic[2] and the Ochsner Clinic[3] were helped manometrically results quite in line with those reported before this society two years ago by Dr Schaffer[4] The surgical statistics cannot of course deal with all the other individuals with hypertension and unilateral renal disease who are not operated upon for one reason or another and if these are in turn diluted with all patients with bilateral renal disease and normal blood pressure the frequency of hyper renal hypertension becomes very small indeed And yet I must admit that the only patients I have seen cured of malignant hypertension have been treated by nephrectomy

Hypo renal Hypertension

It seems significant to me that when clinical hypertension is associated with demonstrable renal disease at all the kidneys are small and not large a circumstance consistent with the appearance of hypertension in bilaterally nephrectomized animals kept alive by peritoneal dialysis[5] or parabiosis[6] At present it is impossible to decide whether this comes about because normal kidneys excrete destroy or inhibit the production of pressor substances from extra renal sources All I intend to do is to describe a few nebulous clues which suggest that the renal tubule normally inhibits the anterior pituitary adrenocortical machine

An impressive piece of evidence has just been reported before the American Heart Association in New Orleans by Skelton[7] who found that malignant hypertension develops in young rats subjected to uni nephrectomy

TWO KINDS OF RENAL HYPERTENSION

By THOMAS FINDLEY M D

AUGUSTA GA

Many of us here remember the rosy glow that hovered over every sphygmomanometer following the publication in 1934 of Goldblatt's classic method for producing sustained diastolic hypertension in animals and the subsequent re-discovery of renin in Cleveland and Buenos Aires The expected therapeutic triumph has not yet appeared however and I suppose it is fair to say that the patient with uncomplicated hypertensive vascular disease is probably no better off today than he was then

It is not for want of effort tho that the origin of this disorder seems as obscure as ever Ingenious and even profitable attempts have been made to implicate the psyche the hypothalamus the autonomic nervous system and certain endocrine glands in its genesis but somehow all roads return to the kidney Oddly enough there is still no agreement as to whether constriction of the renal artery for example results in hyper or hypo function of the kidney insofar as the ensuing hypertension is concerned An explanation by analogy suggests itself however One is reminded of the fact that hyperglycemia of pancreatic origin may be due either to lack of insulin or to excess of glucagon so even the experiment of von Mering and Minkowski is not as simple as it seemed to be when insulin first came to light It begins to look as though high blood pressure may result from two kinds of renal dysfunction

Hyper renal Hypertension

The idea that hypertension is due to an excess of circulating vasoconstrictor material emanating from the kidney is simple and attractive This is so chiefly because abrupt disturbances in renal blood flow produce such an excess and because nephrectomy occasionally reduces blood pressure When one is faced with two alternatives however it is probably wise to choose not the one for which there is the greater number of arguments but that one against which there are the fewer objections Certainly the case for *hyper renalism* became less persuasive when several investigators independently produced hypertension by bilateral nephrectomy

The complicated system of enzymes and substrates known here in the interest of simplicity as *renal pressor substance (RPS)* must have some function however The literature on the subject is enormous and controversial

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hibit water diuresis. In Cushing's syndrome the diuresis proceeds undisturbed much as it does in diabetes insipidus, and in essential hypertension the anti-diuretic effect is only moderate. Thus the capacity of the renal tubule of the hypertensive subject with or without Cushing's syndrome to resorb normal amounts of salt and water is limited and resembles that of a normal subject receiving cortisone in doses too small to produce hypertension or edema. Farnsworth[10] had previously reported that the tubular resorption of chloride is impaired in hypertension. All of this seems paradoxical and obscure, especially in the light of the demonstration by Perera and Blood that hypertensive patients tolerate salt restriction better than normals do.[11] There is some evidence that the hypertensive individual is abnormally sensitive to parenteral DCA, and it is well known of course that this substance produces sodium diuresis in Cushing's syndrome.

Summary

Hypertension due to excessive secretion of a renal pressor substance probably exists but must be rare.

Hyporenalism is a more satisfactory explanation for human and experimental forms of hypertensive vascular disease. A deficit of renal tubular mass or function probably elicits a response from the anterior pituitary-adrenocortical axis because (a) bilateral nephrectomy induces eosinophilia of the anterior pituitary, (b) enucleation of the adrenals produces hypertension only in a uninephrectomized animal, and (c) the kidney in human hypertension handles salt and water loads in a Cushingoid manner.

Human hypertension could be due to a metabolic defect in renal tubular epithelium which renders it insensitive to trophic influences of anterior pituitary or adrenocortical origin.

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uni adrenalectomy and radical enucleation of the other adrenal So far as I know this is the first time that steroid hypertension has been produced by intrinsic mechanisms only and is certainly a convincing demonstration that the adrenal cortex may be implicated in spontaneous disease With Dr Skelton we are examining adrenal vein blood from these animals to see whether the regenerating cortex secretes steroids of abnormal kind or quantity The other part of this phenomenon which interests me particularly is the fact that uni nephrectomy and a high sodium intake are absolutely necessary features Once again the protective influence of normal renal epithelium is demonstrated and that leads to another clue which may or may not be meaningful

Several years ago we reported that a number of procedures which disturbed the blood supply to the kidney also induced eosinophilia of the anterior pituitary [8] Dogs rendered hypertensive by renal artery clamps showed an increase in eosinophiles from a normal value of 40% to a level of about 70% and similar increases followed complete occlusion of both the renal artery and vein for short periods of time At first we were inclined to attribute this to the stimulating effect of *RPS* but the pituitaries of bilaterally nephrectomized hypertensive dogs kindly sent to us by Dr Grollman showed the same changes We inferred therefore that renal tubules normally inhibit the acidophilic elements of the anterior pituitary I am sorry that we have no biologic evidence to show that these cells are secreting increased amounts of renotrophin but endocrinologists seem to accept the feed back principle when applied for example to the increased output of trophic pituitary hormones induced by castration or by thyroidectomy When one kidney is badly damaged or entirely removed its mate enlarges and this compensatory hyperplasia is probably due to growth hormone or to something not yet separated from it Essential hypertension could be caused by an enzymatic defect in the renal tubule which renders it insensitive to these trophic influences The whole process might represent a homeostatic response designed to repair a threatened kidney the reaction persists simply because the kidney cannot respond Ultimately vascular lesions of hormonal origin appear and the organism destroys itself Once more the hope of substitution therapy appears

Finally there is evidence of altered sodium metabolism in the common idiopathic variety of hypertensive vascular disease In Cushing s syndrome the renal tubules reject a surprisingly large fraction of the salt offered to them in glomerular filtrate Birchall *et al* [9] found this phenomenon occurred in essential hypertension also but to a lesser extent and that normotensive subjects behaved this way after small doses of cortisone Furthermore in hypertension the kidney responds abnormally to the Hickey Hare test a procedure which measures the ability of hypertonic saline infusions to in

the excess of salt seems to spill over I do not know why it is that Cushing's disease patients given DCA leak sodium rather than retain it as normal individuals do

All I feel convinced of is that there are three important factors One is a steroid one is a reduction in renal mass and another is the sodium ion I hope I will be wiser in the future than I am today

I do not know anything about aldosterone in this problem Dr Lukens I feel however that one should not demand that an excess of steroids be demonstrated in this situation Removal of the kidney mass might simply sensitize an organism to a normal amount of steroids and this would explain the fact that biochemists have searched for abnormal qualities of hormones in vain It may be a matter of sensitization

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DISCUSSION

Dr John P Merrill (Boston) I am very much interested in Dr Findley s comments particularly about the role of sodium because Grollman s work in renoprival hypertension was first criticized because of the fact that as we all know well it is difficult to keep these animals alive with peritoneal irrigation and at the same time control their salt balance and water balance However Dr Kolff in Cleveland did produce in these same animals severe vascular lesions without hypertension by controlling the salt intake which would fit very well with what Dr Findley has suggested here

In one unfortunate case in whom a single kidney was removed by mistake in an outside hospital we were confronted with the problem of keeping a man alive who had no kidneys whatever for a period of fifty four days We were naturally very much interested in the problem of renal hypertension This boy did not develop marked hypertension over a period of fifty four days without any kidneys but of course to keep him alive we had to restrict his sodium drastically

I wonder what Dr Findley believes the role of sodium is in this situation whether it is simply a matter of increasing the vascular volume or whether it has something specific to do with the vascular disease which develops

Dr Francis D W Lukens (Philadelphia) Since Dr Wolferth and I reported to the Association on the effects of adrenalectomy in hypertension we are interested in the role of sodium retention in this disorder Dr Findley s indirect measurement of sodium metabolism by the water excretion test appears to be a valuable contribution to this topic Is the evidence for faulty sodium metabolism present in all hypertensive patients or only in a few of them? Luetscher has succeeded in measuring aldosterone excretion in various diseases but too little has been done in hypertension to provide any answers

I do not think that pituitary growth hormone (whatever that may be chemically) has much to do with hypertension Dr Jeffers and I gave dogs massive doses of a crude pituitary extract which is now known to be rich in growth hormone without observing any change in blood pressure Will Dr Findley comment on this becaus it would simplify the problem if growth hormone could be eliminated?

Dr Thomas Findley (Closing) Obviously I cannot answer either of the discussants well thought up questions I do not know the role of sodium These people act as if they already had a surfeit of sodium in their bodies maybe that is the reason

the excess of salt seems to spill over I do not know why it is that Cushing s disease patients given DCA leak sodium rather than retain it as normal individuals do

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HEPATIC COMA

A Clinical Study

By MAHLON DELP, M.D., and (by invitation) W. GRAHAM CALKINS, M.D., and ROBERT W. WEBER, M.D.*

KANSAS CITY

Hepatic coma is a clinical syndrome long recognized and variously designated as acholia,[1] cholemia,[2] hepatargie,[3] and most recently, even perhaps most accurately termed portal systemic encephalopathy.[4] In addition to the usual signs of liver failure, the characteristic clinical features in typical hepatic coma include emotional lability, mental dullness, delirium, flapping tremor, distinctive moaning cry, and abnormal neurological signs. The syndrome frequently progresses through irreversible coma to death. Wide variations which exist in descriptions of this syndrome are largely the result of differences in patient material and stages of coma in which the observations have been made.

It was the object of this study to review cases of hepatic coma which were personally observed during the last eight years. Careful attention was given to the detection of the earliest signs suggesting impending coma, since obviously this period should offer the greatest opportunity for its reversal. It seems clear that there is a state or pre-coma or impending coma which precedes true hepatic coma, and it may occur in any type of liver disease. No essential qualitative difference is to be noted in these signs in the patient with acute hepatitis or the patient with diffuse hepatic fibrosis. In both groups, pre-coma symptoms may be transitory and subside without progression into coma.

Deep hepatic coma varies from patient to patient, but the general features in all forms of liver disease are quite similar. Reversibility and recovery is more common in the patient with cirrhosis than in the patient with extensive cellular damage. Pre-coma may be very transitory, persist for days, or progress straight away to deep coma. True coma may appear precipitously or only after many days of pre-coma. It may either be irreversible, resulting in death, or clear completely with apparently no residual. Certain variations in precipitating factors are also noted in the two groups.

Ephemeral as the evidence may be, there persists in the minds of anyone studying these patients features which indicate a common denominator regarding etiology. A diverse pathogenesis may exist in the several forms of liver disease, but somewhere a common causal factor probably exists.

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Patient Material

Patient material for this study is divided into three groups All patients were observed by at least one member of the group (MHD) and followed to autopsy or dismissal from the hospital during a period from January 1947 through August 1955

Group I consisted of forty three patients with liver disease manifesting hepatic coma The following criteria were observed in making the diagnosis of hepatic coma 1) the presence of coma associated with delirium flapping tremor fetor hepaticus or other signs and symptoms usually associated with hepatic coma 2) the presence of primary or secondary liver disease and 3) the absence of any other disease that would adequately explain coma

Very likely some cases of hepatic coma were overlooked or mistakenly omitted even though almost every patient with serious liver disease seen at this hospital during the past nine years has been seen by one of this group (MHD) It frequently is difficult however to determine the cause of coma in patients after massive hematemesis has occurred The same is true in patients with malignant tumors which have spread to the liver and other organs

Group II was composed of one hundred healthy blood donors Blood ammonia levels were determined on these individuals to establish normal values for our laboratory The determination of the blood ammonia concentration was carried out by a modification of Conway s Method[3, 4]

Group III included fourteen patients with liver disease upon whom blood ammonia levels were done Such studies were available only during the last six months of this study and consequently the number of patients in this group is small

Results

The diagnosis of the underlying liver disease in each case is listed in Table I Post mortem examination was done in thirty-one cases and liver biopsy in six others In the remaining six patients the diagnosis was made on clinical evidence

Laennec s cirrhosis or more properly termed diffuse hepatic fibrosis was *present in twenty four patients This is not an unexpected number of such* cases since this disorder is probably the most frequent type of chronic liver disease

The patients were almost equally distributed as to sex there being twenty two females and twenty-one males Eight patients were Negro and thirty five were Caucasian This roughly represents the ratio of admission to this hospital Their ages ranged from eight to seventy five years Three patients were in the first or second decade of life one in the third five in the

TABLE I

Etiology of Liver Disease in Patients with Hepatic Coma

Diagnosis	Males	Females	Total
Laennec's cirrhosis	12	12	24
Post necrotic nodular cirrhosis	4	2	6
Biliary cirrhosis	1	3	4
Infectious hepatitis	1	3	4
Serum hepatitis	1	1	2
Carcinoma			
Primary	1	0	1
Metastatic	1	1	2
Total	21	22	43

TABLE II

Symptoms during Pre Coma Stage

Symptom	Number Patients Whom Present (343 Cases)
Irritability	36
Confusion	30
Delirium	28
Agitation	23
Lethargy and weakness	20
Peculiar cry	19

fourth ten in the fifth sixteen in the sixth seven in the seventh and one in the eighth

Table II lists the symptoms and signs most frequently observed prior to the onset of coma Irritability confusion and delirium ranked in that order as evidence that coma was imminent

Table III lists the most frequent physical findings All but two of the patients were jaundiced at the onset of coma Enlargement of the liver and ascites were the next most common physical findings Thirty-eight patients had a temperature above 99 degrees F Eight of the latter had a temperature above 104 degrees during the illness

Table IV summarizes the neurological signs observed during coma While muscular irritability and muscle tremor are constant features either during pre coma or coma we have seen only one patient actually having convulsive seizures

Tables V and VI show laboratory data on these patients

Biochemical tests of liver function showed significant abnormality in those cases with severe hepatocellular injury In patients with cirrhosis however this was not necessarily true

TABLE III

Physical Signs of Hepatic Coma

Physical Sign	Number Patients in Whom Present (43 Cases)
Hepatomegaly	42
Jaundice	41
Fever	35
Ascites	34
Evidence collateral circulation	33
Liver palms	33
Spider nevi	27
Splenomegaly	19
Flapping tremor	19
Fetor hepaticus	15

TABLE IV

Neurological Signs during Hepatic Coma

Neurological Sign	Number of Patients Whom Present (43 Cases)
Normal reflexes	24
Babinski	
Hypoactive reflexes	
Hyperactive reflexes	4
Absent reflexes	3
Nystagmus	1
Convulsions	1

An analysis of precipitating factors in hepatic coma are presented in Table VII. The most common event preceding the appearance of coma was of bleeding from esophageal varicosities or other undetermined sites in the upper gastrointestinal tract. This occurred in twenty-one cases. Three patients had received ammonium chloride prior to the appearance of coma. One patient had received amino acid preparations intravenously. One had received exchange resins containing ammonium. Grouping these four items together, twenty-six patients had unusual amounts of nitrogenous substances in the intestinal tract before coma developed. Three patients developed pneumonia prior to the onset of hepatic coma. Pre-coma and coma quickly followed paracentesis in three patients. Two instances followed surgery. Coma followed the administration of barbiturates in one, and narcotics in another. In only one case was an alcoholic debauche an incident immediately preceding hepatic coma.

Only four of these patients survived and were dismissed from the hospital. Of the thirty-nine who expired three patients had survived one

TABLE V

Hemoglobin, WBC and Liver Function Studies

Case	Hgb Gm	WBC	SB D	SB T	AP	UU	FU	PT	B m	CC	TT	CE	SA	SG	SI	TC
HF	14 0	6 150	0 7	4 0	2 5	19 8	820	28%		4	18	40%	2 5	3 0	220	175
FA	8 4	6 900	0 8	1 5	5 0	0 7		78%		4	22	50%	4 5	3 5		146
HJ	12 0	3 850	12 0	24	3 0	1	200	48%		4	28	30%	2 5	4	140	200
FR	9 8	5 050		12	33 6		4	29%		4		36%	2 0	4 0		250
HB	14 2	4 350	4 0	7	12 2			55%		1	4	6%	3 0	2 0	45	175
MB	10 7	26 650	5 0	10	10		133	33%		2	10	20%	2 0	3 0		250
TI	11 8	16 600	2 0	5	2 0	0 9		20%		4	20	40%	3 3	3 0	135	200
MMc	13 8	13 600	14 2	36	8 0	4		10%		4	20	30%	3 0	3 0	225	150
CG	8 0	6 250	11 8	19 4	8 0			30%		2	0	10%	2 5	0 3	381	43
LA	12 0	29 650	3 0	16	5			15%		3	9	10%	3 5	3 0	1 0	100
LY	11 3	2 950		12		0	100	10%	85%	4	53	40%	1 0	6 5		100
AC	10 9	10 650	12	16	10	2		14%		3	16	10%	3 5	2 0	56	200
EW	3 4	14 200	8 6	16	2 0					4	10	10%	2 5	3 0		100
PD	11 8	11 550	8 6	14	2 5	3 0		20%		4	20	20%	2 5	3 5	156	100
KS	9 5	4 700		17 5	24	0 3		38%	5%	1	14	40%	1 0	3 5		200
LK	13	6 900	6 8	14		6 0	75	80%	100%	2	24	30%	1 37	3 23		200
IT	12 6	10 200	2	3 5	2 0			10%		4	49	30%	2 0	4 5	70	150
LY	11 4	6 600	15	24	3			12%	20%	4	60	20%	2 5	4 5		175
LT	11 4	5 600	4	4	10			30%	20%	4	12	50%	3 5	3 5		150
JN	11 7	4 750	1 5			4 0	150	30%	65%	4	18	40%	2 0	3 0		98
CB	8 0	10 450	3 0			17 8	40	40%		3	8	50%	2 0	2 5		250
CW	6 0	21 500	1 0	8 2						1	5	50%	1 8	2 6		212
WS	12 3	8 600		2 0				48%	10%	3	7		3 5	2 0		168
WR	9 0	9 200		14						3	5	20%	1 5	3 0		
ZM	13 0	26 000														
NS								18%					2 3	3 2		
LS	12 0	12 800	5 8	10 0	12 1		75	79%	1%	3	13	38%	3 11	2 69		205
WM	11 4	9 800	1 7	4 3	1 9	0 7	130	48%	12%	4	31	47%	2 16	3 54	157	258
BI	9 0	8 800	1 9	6 9	1 6	5 9	126	43%			23	35%	2 84	3 66	212	256
CC	11 0	14 800	24 0	42 2	69 0			100%		Neg	9	6%	2 61	2 39	500	68
MJ	11 2	5 000	0 9	15 7	5 7			41%	47%	4	25	32%	3 36	3 24	110	276
RG	12 5	15 200	3 2	5 0	5 7			75%		Neg	24	45%	2 48	4 82	96	300
AM	11 8	6 650	12 9	21 2	4 2	0 4	5	43%	59%	3	12	22%	3 18	3 42	155	100
LC	7 6	8 250	7 9	14 4				34%					2 38	5 62		
JG	6 5	5 350	0 5	1 7	14			33%		3	4	65%	3 4	1 43	268	23
FMS	9 9	8 000	4 4	8 4	1 9			15%		4	17	23%	2 31	3 39	176	79
RB	10 4	27 100	6 8	10 6	14 3	7 8		43%		3	16	14%	0 64	2 46	102	348
AH	8 7	7 500	7 0	11 5				65%					3 13	1 97		
FN	11 0	6 550	0 5	1 0	6 1			70%	20%	3	24	52%	2 21	3 89	65	276
CI	9 9	19 250	11 3	19 0	7 6					1	17	32%	2 87	3 93		82
JB	11 0	10 350	3 9	6 8	1 5			19%	40%	4	18	39%	2 11	4 9	110	118
FT	12 0	8 400	3 6	20 6	11	0 4	2	27%		4	28	11%	2 0	4 0		200

episode of coma previously One of these died in a second episode One survived the second episode but succumbed to a pulmonary embolus several weeks later The third patient after being in coma thirty-eight hours of his third episode finally succumbed

The blood ammonia concentrations of the one hundred normal blood donors (Group II) is presented in Figure 1 The values ranged from 34 to 133 micrograms with a mean of 79 5 (Standard Deviation 2 68) micrograms per one hundred milliliters Figure 1 shows the percentile distribution of the blood ammonia concentration in this group of one hundred normal persons Only one individual had a blood ammonia concentration below 50 micrograms per one hundred milliliters The blood ammonia of six individuals was over 110 micrograms per one hundred milliliters Since ninety three per cent of this group had blood ammonia levels between 50 and 110 micrograms per one hundred milliliters this range was arbitrarily selected as representing the normal blood ammonia We consider blood ammonia levels between 111 and 135 micrograms per one hundred milliliters to be in a borderline zone between normal and abnormal However values over 135 micrograms may be considered definitely abnormal

Table VIII lists the blood ammonia levels in eight patients with hepatic coma Three patients (PC) (EN) and (GC) had normal blood ammonia levels while the remaining five patients had abnormally high blood ammonia level on at least one occasion

Table IX lists the blood ammonia levels in six patients with liver disease who were not in pre coma or coma states All six had normal blood ammonia levels

Discussion

We use the term hepatic coma because of its widespread use and general acceptance No term so far suggested seems entirely satisfactory although

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Key to abbreviations of tests

SB D Direct serum bilirubin in mgm /100 cc

SB T Total bilirubin in mgm /100 cc

AP Alkaline phosphatase in Millimol units

UU Urine urobilinogen in units in a two hour urine sample

FU Feces urobilinogen in mgm per 24 hours

PT Prothrombin in per cent of normal

Brom Bromsulphthalein 5 mgm per kilo in per cent retained

CC Cephalin cholesterol 0 to 4+

TT Thymol turbidity in units

CE Cholesterol esters in per cent of total

SA Serum albumin in gm /100 cc

SG Serum globulin in gm /100 cc

SI Serum iron in microgram /100 c

TC Total serum cholesterol in mgm /100 cc

TABLE VI

Electrolytes and NPN Studies Correlated with Ascites

Case	NPN	CO	Na	K	Cl	Ascites
MB	117	12 6	111	5 4	89	yes
FY	30	26 6	131	4 6	102	no
MMc	42	21 8	144	5 1	102	no
EA	102	11 9	127	5 0	103	yes
AC	Too high to read	38 2	130	2 6	87	no
PK	34					yes
LT	65	25	127	4 6	113	yes
KS	37	16 8	138	5 0	97	yes
JN	37	28 8	435	mgm % as	NaCl	yes
IT	101	18 5	128	4 5	105	no
WR	33					no
NS	46 6	17 9				yes
EW	70	13 5	132	4 1	89	yes
CB	34	29 4				no
LT	215					no
EY	50	10 6	500	mgm % as	NaCl	yes
CW	30		490	mgm % as	NaCl	yes
WS	30	18 0	128 9	5 3		yes
ZM	105	28 0	360	mgm % as	NaCl	no
FR	60	18 5				yes
TI	44	30 6	127	3 1	94	yes
PD	28	24 7	125	4 5	107	yes
EA	159	25 0	138	5 0	108	yes
HF	56	20 3	132	4 5	105	yes
CG	32 5	23 0	130	4 5	101	yes
HJ	32	22 2	123	5 2	111	yes
HB	33	23 [illegible]	139	4 9	102	no
ES	39	18 5	123	6 3	98	yes
WM	45	11 0	115	8 1	96	yes
BI	32	18 5	123	5 1	93	yes
GC	28 5	17 8	132	4 7	98	yes
MJ	3	20 3	127	4 9	108	yes
RC	63	17 8	122	[illegible] 2	98	yes
AM	35 8	30 6	130	5 9	98	yes
PC	98 (BUN)	14 0	120	9 2	115	yes
JG	55	20 [illegible]	[illegible]	3 [illegible]	126	yes
FMS	46 3	25	131	5 8	94	yes
RB	17 5 (BUN)	16 8	110	6 8	83	yes
AH	42	27 0	131	4 3	90	yes
EN	8 6 (BUN)	23 [illegible]	13	4 3	104	yes
CI	58	20 3	11	5 [illegible]	87	yes
JB	11 0 (BUN)	19 5	128	4 4	91	yes
FT	30					no

TABLE VII

Factors Precipitating Hepatic Coma

Factor	Number (43 Cases)	
Gastrointestinal bleeding		21
Drugs		9
Ammonium chloride	3	
Barbiturates	2	
Narcotics	1	
Acetazoleamide	1	
Amino acid preparation	1	
Cation exchange resins	1	
Infection		3
Paracentesis		3
Surgery		2
Alcoholic debauche		1
No factor identified		4

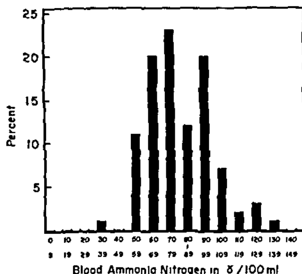


FIG 1 Blood ammonia levels in one hundred healthy blood donors

portal systemic encephalopathy of Sherlock[4] expresses the clearest connotation of the clinical picture and pathogenesis

Liver cell failure may occur in all forms of hepatic disease but is most often associated with cirrhosis and acute hepatitis of viral or toxic etiology Many features may accompany this hepatocellular failure such as jaundice

TABLE VIII

Blood Ammonia Levels in Hepatic Coma

Patient	Diagnosis	Blood Ammonia (Micrograms per hundred milliliters)
I S	Laennec's cirrhosis	130 169 80 254 [illegible] 59
JB	Laennec's cirrhosis	197 90
CP	Laennec's cirrhosis	[illegible]
PC	Postnecrotic nodular cirrhosis	101 70
I N	Postnecrotic nodular cirrhosis	[illegible]
AM	Biliary cirrhosis	141 131
RG	Primary carcinoma of liver	104 108 122 186
GC	Metastatic carcinoma of liver	91

TABLE IX

Blood Ammonia Values in Patients Not in Coma

Patient	Diagnosis	Blood Ammonia (Micrograms per hundred milliliters)
I C	Laennec's cirrhosis	83
JF	Laennec's cirrhosis	74
I S	Laennec's cirrhosis	69
CS	Laennec's cirrhosis	61
I N	Postnecrotic nodular cirrhosis	84
I L	Serum hepatitis	88

ascites endocrine disturbances and circulatory changes This discussion however is limited primarily to certain features of the central nervous system dysfunction

Mechanisms of these neurologic manifestations have been the subject for much study during recent years Sherlock's[57] explanations of the pathogenic factors include 1) portal venous systemic collateral circulation 2) defective liver cell function and 3) nitrogenous substances in the intestine This is the most lucid interpretation yet offered Decreased liver cell function or by passage of intact liver cells through portal venous systemic collaterals gives access for high concentrations of ammonia to the central nervous system

The clinical manifestations of hepatic coma may be divided into stages of pre coma and coma Depending upon the underlying type of liver disease the clinical features may differ

A typical example of the manifestations of the stage of pre coma in severe parenchymal damage is often seen in the young child or adult with acute viral hepatitis The disease may be ushered in with the usual gastrointestinal symptoms and jaundice Within four to five days of onset the

patient may suddenly and surprisingly become irritable emotional complain of severe headache and somnolence Response to questioning may be fairly normal but may also reveal the patient's apparent irascibility and severe irritability Conversational response may be strangely repetitious A characteristic moaning cry often is spontaneously manifested by the patient while apparently sleeping Upon awakening him you may secure no real evidence or reason for the apparent pain Sensory defects and neurological deficit are not present in the pre-coma stage Pre-coma may exist for a matter of several days terminating in complete return to normal or advance to severe coma within a matter of eight to twelve hours

Pre-coma in the cirrhotic patient presents a similar picture but light differences have been observed This patient while showing no signs of worsening of his liver disease may first complain bitterly of his care and the attention he is receiving Such complaints heard from a previously happy patient may be the first subtle evidence of personality changes of pre-coma Again repetitious answers to questions may be obtained Irritability disobedience and obtuseness characterize the patient's mental attitude Aside from slight tremor and muscle twitching neurological findings are minimal All exhibited signs may disappear or progress to coma

Coma in severe parenchymal cell damage and massive necrosis as seen in the child and young adult may present initially as extreme irritability and continue through delirium mania semi-coma and the usually irreversible deep coma Central nervous system dysfunction may be characterized by motor weakness flaccidity spasticity pathological reflexes severe tremors and rarely convulsions Jaundice is usually very deep and fetor hepaticus is common Recovery in this stage is uncommon in our experience

Deep coma in the cirrhotic patient regularly follows a long history of liver disease Usually it is preceded by bleeding infection alcoholic debauche injudicious use of drugs or the presence of abnormal nitrogenous materials in the gastrointestinal tract Most commonly the patient is brought into the hospital shortly after massive bleeding from esophagogastric varicosities Within the next twenty four hours the patient shows small personality alterations becomes irritable perhaps continues to bleed refuses all medications and attention becomes less responsive to stimulation and drops into deep coma The respiration may be deep and labored as in acidosis Jaundice fetor hepaticus and abnormal neurological signs are usually present Electroencephalographic[9] changes are quite characteristic In contrast to the patient with massive hepatic necrosis recovery is not uncommon Such recovery likely points to fairly intact parenchymal liver cells and strengthens the theory of shunting phenomena either through or around the liver allowing access of some abnormal metabolite to the central nervous system

TABLE VIII

Blood Ammonia Levels in Hepatic Coma

Patient	Diagnosis	Blood Ammonia (Micrograms per hundred milliliters)
FS	Laennec's cirrhosis	130 169 80 254 207 59
JB	Laennec's cirrhosis	197 90
CI	Laennec's cirrhosis	127
PC	Postnecrotic nodular cirrhosis	101 [illegible]0
IN	*Postnecrotic nodular cirrhosis*	[illegible]2
AM	Biliary cirrhosis	141 131
RG	Primary carcinoma of liver	104 108 192 186
GC	Metastatic carcinoma of liver	91

TABLE IX

Blood Ammonia Values in Patients Not in Coma

Patient	Diagnosis	Blood Ammonia (Micrograms per hundred milliliters)
LC	Laennec's cirrhosis	83
JF	Laennec's cirrhosis	74
LS	Laennec's cirrhosis	69
CS	Laennec's cirrhosis	61
IN	Postnecrotic nodular cirrhosis	84
LL	Serum hepatitis	88

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responsible for the neurological changes recognized as hepatic coma. Glutamic acid is unique as the only amino acid supporting cellular respiration in the brain. It is also the one substance suggested as having the ability to detoxify and prevent accumulation of ammonia within the brain. Glutamine, the end product of this reaction, was found by Walshe[11] to be present in abnormally high concentrations in the spinal fluid of patients in hepatic coma.

Kirk's[16] study of ammonia metabolism in liver disease twenty years ago was not followed by attempts at clinical correlation until recently. Gabuzda et al.[17] reported the syndrome of impending hepatic coma in patients with cirrhosis given cation exchange resin. Since these resins exchange ammonia for sodium, it was felt they led to an elevated blood ammonia. McDermott and Adams[11] reported a patient in whom an Eck fistula had been produced during surgery for carcinoma of the pancreas. Typical symptoms of impending hepatic coma could be produced by feeding the patient a high protein diet, urea, ammonium chloride or ammonium containing exchange resins. Traeger[18] fed four patients with cirrhosis ammonium chloride and noted higher elevations of blood ammonia levels and more sustained levels than in four normals given the same dose of the drug. White et al.[19] with ammonium chloride tolerance tests demonstrated similar phenomena.

It was felt that ammonium chloride administration led to hepatic coma in three instances (WS, CB and PD). One patient (EA) who had had a portal caval anastamosis received amino acid preparations intravenously following surgery. His post-operative course had been uneventful until that time. On the fourth day while receiving this agent he developed typical hepatic coma and expired shortly thereafter. One patient (TL) had two episodes of coma quickly following the use of exchange resin. He recovered from both episodes only to expire later from pulmonary emboli. Of special interest is patient (HF) who had diffuse hepatic fibrosis with ascites. His course was uneventful until he received acetazoleamide (Diamox) as a diuretic. Within twenty four hours he had developed hepatic coma from which he did not recover.

Acetazoleamide (Diamox) blocks carbonic anhydrase in the kidney and hydrogen ions necessary for the conversion of ammonia to the ionic form are not produced. Without this conversion ammonia produced by the kidney to conserve base is not excreted in the urine but absorbed into the blood. In patients with severe liver damage or shunting phenomenon *abnormally high levels of ammonia might soon be reached.*

Gastrointestinal bleeding is generally recognized as a precipitating factor in hepatic coma. The explanation for this relationship envisions the liver as being much dependent upon the portal blood flow for its oxygen supply and bleeding episodes resulting in disproportionate reduction in

The characteristic features of coma as seen in this group of patients and outlined above is a composite of cases BP CP CA MMc and EN Irritability, confusion lethargy flapping tremor and fetor hepaticus formed the most helpful symptoms and signs in predicting that coma was imminent

Biochemical liver function tests were not helpful in predicting the onset of coma For several years we have been impressed with the value of serum iron determinations in detecting the amount of parenchymal cell damage in patient with liver disease[9, 10] Invariably this value is extremely high in patients with massive necrosis Patient MMc is a good example The serum iron value does give some indication as to the outcome of coma in such a patient The degree of depression of cholesterol esters roughly parallels the elevation of the serum iron and aids in the prognosis of coma in patients with marked liver cell destruction Neither of these values are helpful in the patient with cirrhosis unless death of liver cells occurs The serum iron level in particular may be normal or low in the patient with cirrhosis This was true for instance in the case of FN

It is commonly stated that patients in hepatic coma develop hypoglycemia Hypoglycemia was not observed in any of the patients in this series[11]

The importance of ammonia in the pathogenesis of hepatic coma has recently been emphasized Such relationship was suspected by Matthews[12] in 1922 when he noted coma in Eck fistula dogs after they had been fed on high protein diets Elevated blood ammonia values in both cirrhosis and hepatic coma have been noted by several investigators[4, 13, 14, 15] Two factors seem to be significant in this situation 1) the presence of excessive nitrogenous substances in the intestinal tract and 2) the by passing of parenchymal liver cells by the portal blood with its high ammonia content The patient with massive cellular destruction of the liver can not accomplish normal ammonia metabolism but for a different reason than the patient with cirrhosis Both may and do develop hepatic coma

The liver is the most important single organ concerned with protein metabolism illustrated by its recognized responsibility for formation and deamination of most amino acids Ammonia from the latter reaction is converted to urea by the liver It is intriguing to conjecture that in severe liver disease there is a failure to perform these functions and as a result an unusual accumulation *of ammonia occurs in the blood It is possible that the* toxic ammonia ion through its effect on the central nervous system produces hepatic coma We have also observed certain similarities in terminal patients *with congestive* heart failure and patients with hepatic coma This has led to the speculation that blood ammonia levels in the patient with congestive hepatomegaly may also be elevated

Walshe[13] *theorizes* that an abnormality of glutamic acid metabolism is

Paracentesis should be done with caution and only if indicated by considerable discomfort of the patient. Steroid therapy may be of value in the treatment of hepatic coma.[1,] In four of our cases temporary improvement followed their use.

Walshe[23] has recently reported the successful use of intravenous sodium glutamate in hepatic coma. Two of the patients (JB and ES) who had repeated blood ammonia determinations were treated with monosodium glutamate in addition to the usual supportive measures. The blood ammonia of one of these patients (JB) fell from 197 to 90 micrograms in a matter of four days after receiving a total of eighty six grams of monosodium glutamate. The other patient (ES) was in deep coma for twelve days and would not respond to any stimuli. During the last eight days of her life she (ES) was given twenty three grams of monosodium glutamate intravenously daily. After three days of this therapy the patient came out of coma for a few hours and was able to answer questions. At this time her blood ammonia concentration had dropped from 169 to 80 micrograms. However this patient rapidly regressed back into coma and developed marked elevation of her blood ammonia level terminally. In these two patients the administration of monosodium glutamate resulted in a temporary improvement of the patient's symptoms and a lowering of the blood ammonia level; the eventual outcome, however, was unaltered.

Summary

1. Forty three patients with hepatic coma have been studied at this institution between January 1947 and August 1950 by our group. The symptoms, signs and laboratory findings that we observed in these patients were similar to those previously reported in the literature.

2. In thirty nine cases a factor precipitating hepatic coma was strongly indicated. Twenty one patients had evidence of gastrointestinal bleeding with blood in the intestinal tract prior to the onset of coma. In six patients substances capable of increasing the blood ammonia were given. Therefore a total of twenty seven patients were exposed to situations which would cause an elevation of the systemic blood ammonia level prior to coma. Infection was suspected in three and paracentesis in the same number. Barbiturates and opiates have been listed in two instances.

3. Blood ammonia concentrations were determined in one hundred normal persons. Values between 50 and 110 micrograms per one hundred milliliters were considered normal. Values between 111 and 135 micrograms per one hundred milliliters were considered to be borderline, and values over 135 micrograms per one hundred milliliters were considered definitely abnormal.

portal over systemic flow may seriously impair the already damaged liver parenchyma We feel that a much more pertinent factor is the absorption into the portal blood of breakdown products from blood in the gastro intestinal tract Twenty one of the patients in this series had major bleeding into the gastrointestinal tract prior to the appearance of symptoms of coma

Although the exact mechanism is not clear more and more evidence is accumulating to indicate that increased ammonia levels are important in the pathogenesis of hepatic coma In the limited number of patients in whom blood ammonia levels were determined in this study high values were associated with hepatic coma but coma was found to exist in the presence of normal values also

Other precipitating factors were demonstrated in this study Since some of these may be avoided in future cases their recognition is in itself important as a preventive measure Paracentesis for relief of ascites in liver disease has been frequently followed by hepatic coma and may also be considered a contributing factor in pathogenesis Two of our patients (CP) and (MB) developed coma shortly after paracentesis and another (EY) already in coma became worse

Patients with severe liver disease seem clinically unable to tolerate opiates and barbiturates In three of our patients (MB EY NS) such agents seemed to be contributing factors in the development of hepatic coma

Since treatment of patients in hepatic coma is so woefully inadequate early recognition of the precipitating factors and prevention of this complication is of the utmost importance

In either the case with marked parenchymal cell damage or with diffuse hepatic fibrosis and portal venous systemic shunting diet vitamins attention to fluids as well as certain restriction of activities are necessary While the high protein diet has been advocated for some time there is now evidence to suggest that the protein may need to be restricted in patients with severe liver disease [9] Barbiturates and narcotics should be used only with caution Compounds containing ammonia or those that will increase body ammonia such as acetazoleamide (Diamox) cation exchange resins and amino acid preparations should be avoided

Prevention of gastrointestinal bleeding is in order if possible The use of anti acids and other efforts made for the patient with peptic ulcer are indicated in the patient with known varicosities of the esophagus Quick control of bleeding by tamponade is practical and occasionally lifesaving Once bleeding has occurred clearing the intestine of blood seems logical to avoid absorption of breakdown products

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DISCUSSION

DR STEWART WOLF (Oklahoma City) I wonder if Dr Delp could tell us whether blood in the gastrointestinal tract from circumstances other than bleeding esophageal ulcers with hepatic damage would result in increased blood ammonium

I think that Leon Schiff had a good many people swallow 500 cc of their own blood I believe that these at least physically normal individuals did not show any increase in blood ammonia I wonder if Dr Delp has any data perhaps on individuals who had bleeding from duodenal ulcers Some of his remarks suggested that the elevated blood ammonia might be due not only to the presence of blood in the gastrointestinal tract but the inadequate processing of this blood by the liver because of hepatic damage or by passing If then massive bleeding from a duodenal ulcer in an individual with a normal liver fails to elevate the blood ammonia ammonia determination might be a very helpful differential diagnostic maneuver in massive bleeding and much safer than some of the other maneuvers

Finally I cannot resist one remark Last year in my maiden presentation before this group Dr Bean caught me in a double Latin plural This time I was interested in Dr Delp s distinction between signs and symptoms

Three observable phenomena (a foetid breath a flapping tremor and a peculiar cry) were observed all effector functions one of them detected by the nose one by the eye and both listed as signs but the one detected by the ear was listed as a symptom

DR DANIEL S ELLIS (Brookline) I would like to stress what Dr Delp has already said about the importance of precipitating factors from this phenomenon which he has just discussed

This has been so apparent that in our cases we have divided cases of hepatic coma into two groups those in which there are precipitating factors extraneous to the liver disease itself and to that group in which there seems to be progressive liver disease and no precipitating factor

This we feel is important because in the group in which there are precipitating factors the chance of helping them and their chance of recovery is indeed much greater than in the group who go into hepatic coma because of progressive liver disease without precipitating factors which we can identify

In addition to the precipitating factors mentioned I would like to add and stress as important that in caring for patients with borderline liver compensation one has to be very careful about protein intake in the diet More protein intake than these people s livers can handle is enough to precipitate hepatic coma and that is very important when it comes to treatment

Our results from the treatment with glutamic acid have been encouraging in contrast to what Dr Delp has said We cannot always correlate improvement with the administration of glutamic acid but there are patients in whom without any question we can reduce the blood ammonia level by giving glutamic acid

In those patients in whom there is an extraneous precipitating factor reduction

4 Present concepts as to the role of ammonia in the pathogenesis of hepatic coma have been reviewed The correlation of blood ammonia levels in fourteen patients in our own material have been presented

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In those patients in whom there is an extraneous precipitating factor reduction

of the blood ammonia level follows glutamic acid administration and whatever else takes place in the normal course of events and these patients are likely to go ahead and get well

In patients who are in hepatic coma because of their severe liver disease without known precipitating factors we can reduce the blood ammonia level by the administration of sodium glutamate intravenously but they may go ahead and die even though their blood ammonia levels return to a more nearly normal level

DR JOHN P MERRILL (Boston) I would like to ask Dr Delp about the mechanism by which diamox raises the blood ammonia level This has a very fascinating bearing upon a controversial aspect of renal function because there is a very vigorous debate about how ammonia gets into the urine

We know that diamox suppresses hydrogen ion secretion and if it is true that ammonia does not get into the urine simply because the urine is no longer acid and is therefore returned to the blood as would be indicated by Dr Delp s observations this is extremely important to people who argue about this problem in renal physiology If it were possible for him to quantitate the rise in blood ammonia with the decrease in urinary ammonia this would go a long way to solving the problem

DR WALTER L PALMER (Chicago) May I ask if any observations have been made by Dr Delp on the effect of choline on the fetor and on blood ammonia

DR MAHLON DELP (Closing) Dr Wolf thank you very much

Dr Wolf we have done blood ammonia levels on patients with bleeding peptic ulcers and we have found no increase in the blood ammonia levels in those patients

I have chosen to interpret that in the same manner of course as Dr Sherlock has with her ammonium chloride tolerance tests which she has done on normal individuals and again on patients with severe parenchymal liver cell damage and in patients who have portal systemic shunting

In those latter individuals the blood ammonia levels increased rather rapidly with ammonium chloride administration in the normal individuals the blood ammonia levels remained essentially normal

Theoretically of course the intact liver cell is able to metabolize this agent and in those patients who had normal livers the ammonia levels have been perfectly normal

With regard to Dr Ellis remarks I have been somewhat encouraged perhaps not as pessimistic as I indicated by the use of glutamic acid I do believe that the chance of its being helpful is greater in the patient who has cirrhosis than in the patient with severe cellular damage

I have only in the past week been through an experience in which an alcoholic with cirrhosis had massive gastric bleeding Within thirty minutes from the start of the bleeding esophageal tamponade had been successfully instituted but coma followed in twenty four hours With the administration of sodium glutaminate the patient came out of his coma in about eight or nine hours and has remained perfectly all right The tamponade now removed the patient is up and about the ward

I cannot answer Dr Merrill s question and comments concerning diamox As I indicated I was a little skeptical about including it here but we have seen several patients in whom the evidences of pre coma followed quickly its administration This has occurred in patients with chronic hepatic fibrosis who were given diamox to produce diuresis

I have assumed that this agent blocks carbonic anhydrase in the kidney and hydrogen ions necessary for the conversion of ammonia to the ionic form are not produced Without this conversion ammonia produced by the kidney to conserve base is not excreted in the urine but absorbed into the blood In patients with severe

liver damage or shunting phenomena high levels of ammonia might be reached Regardless of our inability to clarify the process we still have the firm clinical impression that coma may be precipitated by this substance

I think there was one other comment that was Dr Palmer's comment about hepatitis I have noticed patients in the past who received various lipotropic agents particularly methionine who developed fetor hepaticus as well as other signs of precoma shortly after We no longer permit the use of these agents on any such patients without careful observation and we have not for a good long time

I think Dr Walsh's work reported only a few weeks back in which he attempted to explain this peculiar odor which is so characteristic of serious liver damage may be a clue as to why it does intensify both fetor hepaticus and why perhaps it actually interferes with ammonium metabolism as he indicated

We believe that the outlook in hepatic coma in the patients with cirrhosis of *the liver with simple portal systemic shunting is always much better than it is in* patients who have severe cellular damage I do not mean the ordinary patient with infectious hepatitis who usually recovers rather promptly but the patient with massive necrosis

THE EFFECT OF VENOUS SHUNT SURGERY ON LIVER FUNCTION IN PATIENTS WITH PORTAL HYPERTENSION

(A Follow up Study of 125 Patients Operated Upon in the Last Ten Years)

By DANIEL S ELLIS M D ROBERT R LINTON M D
(*by invitation*) and CHESTER M JONES M D

BOSTON

One of the most encouraging developments in the treatment of liver disease in the past ten years has been the perfection of surgical techniques that relieve portal hypertension and reduce the hazard of bleeding from esophageal varices The most commonly advocated procedure is a veno venous anastomosis shunting blood from the portal into the systemic circulation [1] We have had over ten years of experience at the Massachusetts General Hospital in attempting to relieve portal hypertension by venous shunt surgery and it is important now to assess the results of this therapy and to determine its effect on liver function

The data presented is that resulting from the study of 125 patients who have had 150 technically completed shunt operations in the period from March 1945 to November 1954 All of the survivors now living have been followed for at least twelve months and the longest follow up is ten years Esophageal varices were demonstrated by x ray preoperatively in each patient and this has been accepted as proof of the existence of portal hypertension After the exclusion of other causes of upper gastro intestinal bleeding the varices were felt to be the source of hemorrhage for which shunt surgery was indicated The majority of these patients have been operated upon by Dr Robert Linton and they have all been followed personally by one or more of us

Type of Shunt (Table I)

Eighty-eight of these patients have had a splenectomy and a splenorenal anastomosis The eventual mortality in this group of patients has been 21 deaths or 24 per cent Thirty seven patients have had a direct portacaval anastomosis with a final mortality to date of 15 deaths or 40 5 per cent

In the splenorenal group a total of 10 patients or 11 per cent have died of liver failure compared to a total death of 10 patients or 27 per cent who have died of liver failure after a portacaval shunt This difference in mor

From the Departments of Medicine and Surgery of the Massachusetts General Hospital Boston Massachusetts

TABLE I

Type of Venous Sh nt I oced re in 125 I atients with I o tal Hypertensi n

Type f Oper t	T tals	Death
Splenorenal	88	21 (23 8%)
Direct portacaval	3	15 (40 5%)
Makeshift	5	1 (?0%)
Totals	130	3

There were five more procedures than patients because five patients had two types of shunts constructed

tality plus a similar higher morbidity in our patients after portacaval shunts has made us prefer to do the splenorenal shunt when possible in spite of the fact that the incidence of recurrent bleeding was slightly higher in the splenorenal group

There were 5 so called makeshift or lesser shunts These shunts have been anastomoses between lesser tributaries of the portal circulation and the inferior vena cava the left adrenal and the left ovarian vein These were made in patients in whom it was found impossible to utilize the portal vein or in those who had had previous splenectomies In general it is said that these shunts have limited value and none of them is apt to be as satisfactory as a splenorenal or direct portacaval shunt

Pathological Diagnosis (Table II)

In assessing the effect of the operations on liver function it is important to review the pathology in the liver at the time of operation A wedge

TABLE II

Pathological Diagnosis at Operation in 125 Cases of Portal Hypertension

	N C es		N Dead
Normal liver		19	3 (15 8%)
Portal cirrhosis		98	
Alcoholic type	20		10 (50%)
Post necrotic type	31		11 (3?%)
Unclassified	47		12 (25 5%)
Biliary cirrhosis		4	1 (25%)
Miscellaneous		3	
Sarcoid	1		0
Focal hepatitis	1		0
Chronic peri hepatitis	1		0
No Biopsy		1	0
Totals		125	37 (?9%)

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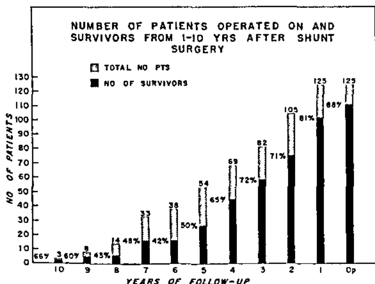


FIG 1 The column at the right represents 111 of 125 patients surviving the operative procedure

from in 3 2 1 and 1 years respectively Two patients out of the group have been completely lost to follow up since their operation

Previously published results of Blakemore[4] Linton[5] and Child[6] prove conclusively the effectiveness of this type of operation in preventing massive esophageal bleeding One of the big questions which has gone unanswered up to the present time is whether or not this type of surgery significantly prolongs the life of these patients beyond the first year after their operation As will be seen from the following data we believe that it does do just this

Figure 1 demonstrates the total number of patients with shunts completed and the total number of survivors in each of the successive years from 1945 through 1954 Thus it is seen that out of three patients operated upon ten years ago 2 or 66 per cent are still living of fifty four patients operated upon at least five years ago 27 or 50 per cent are still living and of one hundred twenty five patients 102 or 81 per cent lived one year It can also be seen from this chart that 111 patients or 89 per cent survived operation leaving nine patients who died within the first twelve months after surviving operation These data show without any question a significant increase in survival in the first year after operation in these patients as compared to the previously reported survival of 50 per cent[7] and 28 per cent[8] of non operated cases after esophageal bleeding

Fully recognizing the possibility that the two groups of cases may not be entirely comparable it is of interest to compare the survival figures of

biopsy was obtained for histological study in each patient. Nineteen patients had no demonstrable liver disease microscopically and are believed to have had extra-hepatic portal bed block as the cause of their portal hypertension. An additional patient whose biopsy was lost before it reached the Pathology Laboratory has been clinically classified as having extra-hepatic portal bed block. A total of 98 patients had a portal type of cirrhosis and these have been subclassified as 20 alcoholic type, 31 post-necrotic type and 47 unclassified type. There were 4 patients with biliary cirrhosis and 3 with miscellaneous types of "hepatitis."

Mortality

The immediate operative mortality has been reported in detail[4] and it will be sufficient to mention here that there were fourteen operative deaths and that this represents an operative mortality of 11 per cent. Subsequently twenty-three patients have died. Of those patients with normal livers only 3 have died and none of them from liver failure. This represents a mortality for this group of 16 per cent. In the alcoholic cirrhotics there was a total mortality of 50 per cent. The post-necrotic group has a total mortality of 32 per cent, which does not bear out the widespread feeling that post-necrotic cirrhosis has a worse prognosis than other types of portal cirrhosis. There has been a 25.5 per cent mortality in the unclassified group to date. One out of four (or 25 per cent) patients with biliary cirrhosis is dead and there have been no deaths in the miscellaneous group. This then represents a total mortality over the ten-year period of 29 per cent.

In reviewing the causes of late death (Table III) it is interesting that only twelve of these patients have died of liver failure and only two from further esophageal bleeding; six died from cardiovascular disease, and one each from pulmonary disease, renal disease and intestinal obstruction.

Survival

At this time 82 patients are known to be alive and have been in direct communication with us in the last three months. Four have not been heard

TABLE III

Late Deaths following Shunt Surgery

	Normal Liver		Cirrhosis		Total
	Splenorenal	Portacaval	Splenorenal	Portacaval	
Liver failure				5	1
Hem. from varices			-		2
Cardiovascular dis.	1	1		4	[illegible]
Pulmonary disease	1				1
Renal disease				1	1
Intestinal obst.			1		1

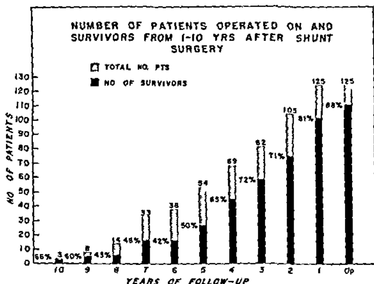


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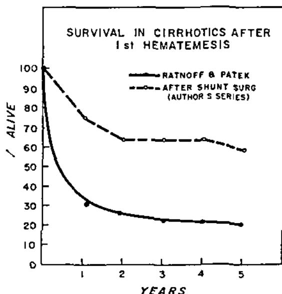


FIG 2 Five year survival curve of 35 cirrhotics after shunt surgery for esophageal bleeding

Ratnoff and Patek[7] in 106 cases of cirrhosis after their first episode of bleeding with the survival figures in our group of patients Ratnoff and Patek reported a survival of only 30 per cent at the end of the first year and 20 per cent at the end of five years Figure 2 superimposes the survival curve of the thirty six cirrhotics in our group of 125 patients who have had shunt surgery after hemorrhage from esophageal varices and who have been followed for at least five years on the original curve of Ratnoff and Patek [7] The decreased mortality is striking in the operated group and shows a survival of 75 per cent of patients at the end of the first year compared with 30 per cent in the non operated cases and 57 per cent at the end of five years compared to 20 per cent in the non-operated group Though the number of cases in this series of cirrhotics who have been operated upon after bleeding and have survived to be followed for at least five years is relatively small we believe that the increased longevity of this group as compared to 30 per cent survival after five years in other reported series of medically treated cirrhotics is highly significant and encouraging [7, 9]

Incidence of Bleeding

Table IV gives data regarding the incidence of postoperative esophageal bleeding in the patients under study From this it is apparent that 18 or 15 per cent of these patients have had some degree of bleeding post operatively There have been only two fatalities from esophageal bleeding

TABLE IV

Summary of Postshunt Esophageal Bleeding

Type of Shunt	Number Operated	No. with Bleeding	No. Dead from Bleeding
Normal livers (5)			
Splenorenal	14	2 (14 3%)	
Portacaval	[illegible]	0	
Makeshift	3	3 (100%)	
Cirrhosis (13)			
Splenorenal	[illegible]4	1[illegible] (1[illegible]%)	[illegible]
Portacaval	30	1 (3%)	
Makeshift	2	0	
Totals	1[illegible]	1[illegible] (14 9%)	[illegible]

postoperatively representing a mortality of less than 2 per cent This figure is much smaller than any expected mortality from esophageal bleeding in patients that have not had shunt surgery The incidence of post shunt bleeding in the patients with normal liver biopsies has been 26 per cent compared to 12 per cent in the cirrhotic group The incidence of bleeding has been larger in the splenorenal group than in the portacaval and greatest in those patients who have had makeshift shunts

Status of Varices after Shunt Surgery

From the beginning it has seemed to us that if one could successfully reduce portal hypertension by performing a venous anastomosis between the portal and systemic circulations one should see a decrease in size or disappearance of esophageal varices We have the results of the post operative roentgenologic examination of the esophagus in 76 of these patients and these results (Table V) are most encouraging and correlate very nicely with the decreased incidence of bleeding previously mentioned

There has been a marked reduction in the size of varices in 81 per cent of the patients who had splenorenal shunts After 37 per cent of these

TABLE V

Status of Varices after Shunt Surgery

	Splenorenal	Portacaval	Makeshift	Total
Number examined	54	19	3	[illegible]6
No varices	20 (3[illegible]%)	9 (4[illegible]%)		[illegible]9 (39%)
Smaller	24 (44%)	[illegible] (3[illegible]%)		31 (41%)
Unchanged	[illegible]	3	3	13
Larger	3			3



FIG. 3. X-rays of the esophagus in a patient with portal hypertension illustrating the presence of large varices before splenorenal anastamosis and virtual disappearance of varices sixteen months after operation.

shunts no varices were demonstrated. Eighty-four per cent of the portacaval shunts show similar diminution in size of varices and in 47 per cent of these shunts there were no varices demonstrated. There was no evidence of reduction of the size of the varices in any of the makeshift shunts which we have been able to examine postoperatively.

Figure 3 shows rather dramatically the disappearance of varices after shunt surgery in one of these patients, and to our minds is irrefutable evidence that the portal pressure is markedly reduced in patients on whom successful shunts have been performed.

Figure 4 is of interest in that it shows another patient with extensive varices before operation; the center x-ray still shows the presence of varices two weeks after the shunt, and the x-ray on the right shows the esophagus to be free of demonstrable varices in the same patient two years after operation. In the early days of our experience with this operation we were



FIG 4 Esophageal x rays in a patient with portal hypertension before two weeks after and two years after portacaval shunt Varices are still present two weeks after operation but have disappeared in the x ray taken two years after operation

x raying our patients in the immediate postoperative period and were disappointed to find no evidence of diminution in the size of the varices We have subsequently learned as Figure 4 demonstrates that it takes some time for the varices to disappear or become smaller

Liver Function

We have personally examined 52 of those patients now living and reviewed reports from the remaining 30 and or their present physicians As a result we have classified them into three groups The first comprises 55 patients who are doing well carrying on a full program of work or household duties and without any important physical limitations of which they are aware The second group comprises 21 patients who are reasonably active but with some definite limitation Nine of these have limitations due to progressive cirrhosis 7 are handicapped by recurring episodes of bleeding and the remaining 5 have disease unrelated to their liver disease or portal hypertension The third group comprises 6 patients each of whom is incapacitated by cirrhosis of the liver Out of 82 living patients only 15 or 18 per cent have enough disturbance of liver function to cause them to be aware of some degree of incapacity

We have obtained laboratory data on the liver function of as many of the living patients as possible (Table VI)

Of 62 determinations of the *serum albumin* level 29 per cent are higher

TABLE VI
Liver Function after Shunt Surgery

	Albumin	C ph Floc	S r B L	B S P
Total no determined before & after	62	61	61	48
Improved	29%	40%	30%	23%
Same	53%	40%	50%	31%
Worse	18%	20%	20%	46%

53 per cent are equal to and 18 per cent are lower than the preoperative levels in the same patients In determining these figures we have considered a change of 0 5 gms % to be a significant change Eleven patients have levels below 3 gms % *Nine of these were classified in group 2 or 3 above* and only two of them are in group 1 and doing well without limitations

Total *serum bilirubin* determinations are available for preoperative and follow up comparison in 61 patients Thirty per cent show improvement *50 per cent are the same and 20 per cent have increase in their bilirubin* levels A change of 0 5 mgs % in this determination has been considered significant There are 20 patients who now have bilirubin levels 1 5 mgs % or higher There appears to be no important correlation with the results *of this test and the clinical grouping above*

Cephalin flocculation determinations in 61 patients reveal that 40 per cent show improvement 40 per cent remain the same and 20 per cent are worse than before operation An increase or decrease of 1+ at 48 hours in *this test was considered a significant change There are only 2 patients* with a cephalin flocculation of 2+ or less who are not doing well Of 14 patients with a 4+ test 12 have other evidence of poor liver function and 2 are clinically doing well

Bromsulphthalein determinations (5 mg /kg) have been checked in 48 patients It was not done in patients that were obviously jaundiced A change of 5 per cent retention at 45 minutes has been considered significant Twenty three per cent of the patients show improved results 31 per cent *no change* and 46 per cent show increased impairment of this functional test One cannot rely solely on this test as a guide to determine the well being of the patient

It is of interest that the hemoglobin determination in 74 patients is 12 grams or better in all but 10 of them and in only 3 is it below 11 grams Each of these three have continued to have recurrent gastrointestinal bleeding

The lack of available standards for a similar group of non operated cases makes evaluation of the laboratory data difficult It seems clear that there is no proof in these data that venous shunt surgery in itself leads to

more impairment of liver function than would normally occur in patients with portal hypertension This probably does not hold true in cases that have little liver dysfunction to begin with and in whom adequate collateral circulation has not developed before shunt surgery An important number of the patients have improved liver function as shown by the results of the tests just reported

So much for the evaluation of liver function as measured by these laboratory tests One of the most striking things that we have noticed in addition to the decreased incidence of bleeding has been the dramatic clinical improvement in a large number of these patients after their operation Such improvement had not occurred before operation even in the face of prolonged good medical treatment The changes include improved feeling of well being and strength improved general appearance with restoration of normal skin color return of normal fullness of face and normal musculature with surprising weight gain regrowth of previously sparse axillary and pubic hair and in some cases disappearance of ascites and edema Figures

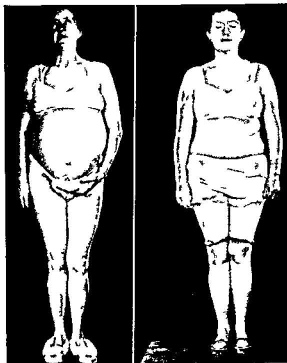


Fig 5 Left Patient before operation after 2 years of medical treatment Right Same patient six months after splenectomy and splenorenal shunt

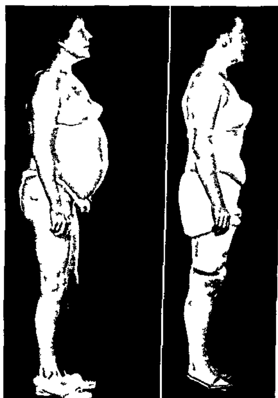


Fig 6 Profile views of same patient shown in Fig 5

5 and 6 illustrate clearly these changes in one of our patients It is of interest that this clinical improvement is not necessarily accompanied by appreciable improvement in the liver function tests

There is experimental evidence that relief of portal pressure produced in dogs will lead to marked weight gain and general clinical improvement in these animals[10] We believe that we are seeing the same sort of thing perhaps to a more marked degree in many patients whose portal hypertension is relieved by venous shunt surgery As Bollman has also suggested it is quite possible that this procedure leads to improved physiology in other organ systems such as the small intestine as well as in the liver itself

In conclusion we believe this to be a most important group of cases and recognize that they will have to be followed closely for another five years before many of our questions about them and about the value of this form of therapy will be conclusively answered At the present time however we are convinced that shunt surgery can be performed in patients with serious liver disease at a reasonable risk and that such surgery can relieve

portal hypertension and markedly reduce the incidence of bleeding from esophageal varices By accomplishing this the length of life of the e patients is increased and in the majority their state of health is improved The improvement of liver function as measured by the tests employed is apparent in many cases but is seldom commensurate with accompanying clinical improvement This is due to the fact that our tests are but crude measurements and we u pect to the fact that there is improved physiol ogy elsewhere in addition to that in the liver itself

Summary

1 We have reported the follow up studies on 125 patients who have had portacaval or splenorenal shunts for portal hypertension

2 The length of follow up is one to ten years

3 The overall mortality is 29 per cent The operative mortality is 11 per cent

4 By comparison with other reported non operated series the incidence of bleeding is markedly reduced and life is prolonged

5 Of 76 cases re-examined by roentgenological study 80 per cent have been shown to have reduction in the size of the esophageal varices Thi we interpret as evidence of reduced portal pressure

6 In addition there may be demonstrable evidence of improvement in liver function clinically and by laboratory test

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DISCUSSION

DR. MAHLON DELP (Kansas City): I certainly agree with Dr. Ellis that this is an extremely significant group of patients. I am amazed at the figures which have to do with the mortality because I am ashamed to say it is much, much better than our results. It must be because they are not only skillful but have had a team approach for a long time.

I would like to know, Dr. Ellis, how many of these patients had ascites and in this one in whom you demonstrated improvement and loss of the ascites, what the explanation was.

We have also had a controversy for a long time as to the best clinical method of recognizing esophageal varicosities. I wonder if you use the esophagoscope or the x-ray for this diagnosis.

Lastly, I would like to ask how many of these patients who have had the shunt have since developed hepatic coma or recognized precoma.

DR. F. TREMAINE BILLINGS, JR. (Nashville): I gather from Dr. Ellis' paper that the chief indication for a shunt has been recurrent or first episodes of bleeding from varicosities. He has indicated, however, that improvement has occurred in the incidence of ascites following these operations. I wonder if he has reached a point in his observations where he is willing to recommend the shunt operation for patients who have had no bleeding but who have had recurrent, rather debilitating chronic ascites.

DR. WALTER L. PALMER (Chicago): This is a very important study.

I would like to ask Dr. Ellis if he would be good enough perhaps to repeat what he said, or say a few words about the relative values of the spleno-renal shunt and the portocaval shunt. I thought, as I followed the slides, that you showed a lower incidence of recurrent hemorrhage from the portacaval, but, on the other hand, I thought you showed a higher mortality rate from that.

DR. GEORGE S. MIRICK (Baltimore): I would like to ask Dr. Ellis a little about the criteria for selecting the patients, whether any appreciable number are eliminated as bad risk patients when hemorrhage, let's say, is the indication for operation, and, if this is true, how this might affect the comparison between the prognostic figures of Ratnoff and Patek's natural history study and the prognosis of the patients he has reported on today.

DR. EDWARD ROSE (Wynnewood): I wonder if Dr. Ellis would say something about the causes of immediate postoperative mortality in the 11 per cent who did not survive.

DR. RICHARD B. CAPPS (Chicago): The question as to what type of shunt is the best is rather complicated because there are, of course, a great many factors and considerations involved.

One of the problems which we run into concerns the question of hypersplenism with an increased rate of destruction of red cells and often associated anemia and an increased level of serum bilirubin.

In several cases which have had portocaval shunts we have noticed that hypersplenism actually seemed to be precipitated. It appeared that lowering the portal pressure stimulated splenic activity, producing jaundice and anemia with reticulocytosis and other evidences of hypersplenism. We have felt that one of the advantages

f doing the splenorenal shunt rather than the portocaval was the elimination of the spleen

I wonder if Dr Ellis would make a few remarks about that

DR DANIEL S ELLIS (Closing) It looks like I have to give another paper

Dr Delp you asked how many patients have ascites preoperatively Is that your question?

As nearly as I can recall without referring to the data about seventeen of our cases had ascites at the time they came into the hospital before operation Forty one patients have a history of ascites sometime prior to their shunt surgery

The explanation as to why ascites disappears following shunt surgery is still not settled We hope some day to have the answer It has been said that ascites disappears in these patients because they are getting good medical treatment and that it has nothing to do with the operation I am sure that this is not the only explanation and I am sure that the operation itself is a factor in some cases

I can tell you this We have chosen two patients for operation who have not had bleeding but who have had recurring ascites which has not responded satisfactorily to any form of diuretic therapy and other forms of medical management Contrary to our general feeling that shunt surgery should be reserved for those patients who have bled from esophageal varices we undertook to operate on these two patients because Blakemore has stated that ascites may disappear following the operation

In each instance those patients have done well There have been two other cases which I know about in our hospital in which a shunt has been performed in which there has been no improvement in the ascites

So in answer to your question and to Dr Billings question along the same line I firmly believe that there is a group of patients with ascites who will be benefited by shunt surgery We do not know enough yet to be able to choose ahead of time which ones those are but we are working on just that project For the present we still feel that in most instances a patient should not be subjected to a portal shunt unless he has had his first episode of bleeding You asked how many patients developed coma in the post operative period I think there were about sixteen of them and of these eight recovered and left the hospital

Dr Palmer you were exactly correct in your interpretation of the slides We have had a greater incidence of bleeding in our cases which have had spleno renal anastomoses and we have a higher mortality both operative mortality and subsequent long range mortality in the portocaval group

I for one have favored the spleno renal shunt because of the increased mortality and the increased morbidity in those patients having a direct porta caval shunt

Dr Capps brought up the question of hypersplenism I am sure that this is one of the organ systems which I referred to in which there is improvement following splenectomy and spleno renal shunt

I have not seen Dr Capps development of signs of hypersplenism following a portocaval shunt I am told by some of my surgical colleagues that if you do a porto caval shunt the signs of hypersplenism may disappear even though you have not touched the spleen This is yet to be proven to me I think that in many of these cases we do relieve their hypersplenism and that by doing so their general health is greatly improved That is another reason I prefer the spleno renal shunt with splenectomy to the portocaval shunt

Dr Mirick asked about the criteria for selection of our patients It has been stated (or we have been accused) that this group of patients which I have reported is

a selected group of cases and it does not include the very ill patients who might be seen in such places as the City Hospital or even on our general medical wards

Dr Linton and I feel that this is not a just criticism We have never refused to do a shunt on any patient with recurrent bleeding as long as he was conscious and not in complete hepatic failure

Dr Rose asked about immediate postoperative mortality These figures have been given in detail and reported by Dr Linton There were fourteen patients who did not survive the operation to leave the hospital—I am not sure I can remember them all There were 5 who died of diffuse hemorrhage in the operative field there were two patients who continued to bleed from varices and exsanguinate in the six hours immediately after surgery There was another group I think of perhaps six or seven patients who died in hepatic coma and hepatic failure and never recovered from the operation That is as well as I can remember them without my tables

I guess I have answered Dr Capps question

REOPENING THE CASE OF THE ABDOMINAL AORTIC ANEURYSM*

By IRVING S WRIGHT M D AND (*by invitation*) ENRIQUE URDANETA M D AND BARBARA WRIGHT B S

NEW YORK

Until recent years the problem of the abdominal aortic aneurysm was of academic interest only The diagnosis once established by physical examination or laparotomy was accepted with a reaction of fatalism toward the future The rate of progress was uncertain but the life span was shortened and in some cases death occurred within a few weeks or months On the other hand for reasons unknown there were patients who survived for 5 years or longer There was no known treatment It was recognized that while most thoracic aneurysms were syphilitic in origin the greater percentage of abdominal aneurysms were on the basis of atherosclerosis The majority of these involve the *lower* abdominal aorta which will be used in this paper to signify the portion below the renal arteries This interesting phenomenon was clearly shown in Blakemore's[1] series of 365 cases of aortic aneurysm Of the 192 syphilitic aneurysms 182 involved the thoracic aorta while only 10 involved the abdominal aorta whereas of the 142 arteriosclerotic aneurysms 114 involved the abdominal aorta while only 29 involved the thoracic segment Of 30 miscellaneous types including mycotic traumatic and unclassified 15 were thoracic and 13 abdominal in location Two were unclassified The reason for this anatomical predilection has never been completely clear but the explanation of Blakemore is worthy of careful consideration He suggested that the explanation of the development of aneurysm due to atherosclerosis of the lower abdominal aorta was due to several factors as follows

1 Widespread atherosclerosis tends to involve the entire aorta including the lower abdominal segment

2 The pressure of pulse waves striking the aortic bifurcation and the iliac arteries tends to produce a reverse wave which meets the oncoming next pulse wave This results in a hammerhead of pressure with a sideways thrust and stress on the aortic wall which is not well supported by sheathing or surrounding tissues at this point

3 This stress may be aggravated by the fact that the aorta is fixed at the diaphragm and by the iliac fascia Between these two fixed points the aorta tends to elongate with atherosclerosis It usually deviates to the left This bending tube tends with further strain to dilate into a fusiform

* This report does not include a consideration of dissecting aneurysm

aneurysm This lack of fixation and the deviation forward also explains why erosion of the spine and radiculitis is rare in abdominal aneurysms as compared with thoracic aneurysms

While these may be logical explanations for the location of atherosclerotic aneurysms in the abdominal aorta they fail to explain the predilection of the spirochete for the thoracic aorta This has been held by some to be related to the lymphatic system arrangements but this must be considered as speculation rather than fact

With the development of surgical procedures which render the abdominal aortic aneurysm subject to attack it seems justified to attempt a critical evaluation of the situation as it exists presently The results of surgery are striking often spectacular but are not universally successful Why? This presentation will be an attempt to examine the questions dealing with prognosis symptoms signs and other means of diagnosis selection of cases indications and contraindications effects of location extent and type of aneurysm pre and postoperative care and surgical technics (briefly)

Prognosis —In order to justify this relatively radical surgery it is necessary to establish that the outlook for the patient is poor without surgical intervention and that such an approach offers a reasonable chance for improving this outlook At present the view is held by some surgeons working in this field that most of these patients have a life span of less than two years after discovery of the aneurysm They reason therefore that operation is imperative and should be done with minimum loss of time citing examples of patients who have died from rupture of their aneurysm before they could be operated upon On the other hand there are many internists and general practitioners who take a rather casual attitude towards these aneurysms after their discovery They cite patients who have lived for many years with an aneurysm without much progression or rupture It is probable that to date most of the series of cases reported by surgeons fail to represent the true picture in this regard since patients who are having pain *increase in the size of the mass or other signs associated* with expansion of the aneurysm are especially apt to gravitate toward the surgeon as compared to those who are symptom free

One of the most revealing articles in this regard is that of Estes reporting experience of the Mayo Clinic [2] The prognosis of 102 cases was as seen in Table I From this it is seen that approximately 58 per cent survived 2 years only 19 per cent survived 5 years and 10 per cent survived 8 years It should be remembered however that the mean average age of this group of patients was 65 years at the time of diagnosis so the expectant mortality during the subsequent years would naturally be high Estes reported that the mortality of patients with abdominal aneurysm was consistently higher than that found in comparable groups without such aneurysms In

TABLE I (*Estes*)

Years	Total	Patients Traced	Survival Beyond Period	
			Number	Per Cent
1	102	91	61	67
2	84	74	43	58.1
3	74	63	31	49.2
4	62	52	14	26.9
5	46	37	7	18.9
8	25	20	2	10.0
10	11	8	0 (based on data of 8 traced cases)	

TABLE II

Life Expectancy (Wright et al)

No. Patients Surviving	Per Cent	Duration in years
41	60.3	Less than 1
27	39.7	1
20	29.4	2
11	16.2	3
8	11.8	4
3	4.1	5
3	4.1	6
0	0.0	7

Total traced patients—68 (not operated)

his series the cause of death in 49 of the 64 known dead was as follows 31 (63.3%) died from rupture of the aneurysm 18 (36%) died from other causes In our series of 68 patients who have been investigated for life expectancy the findings were as found in Table II They show that 39.7 per cent lived less than one year after the diagnosis was made Only 20 or 29.4 per cent were alive at the end of 2 years Eight or 11.8 per cent lived 4 years and less than 5 per cent lived 5 years

These figures indicate a prognosis comparable to many forms of cancer and the condition must be recognized as a malignant one

On the basis of these experiences the use of a fairly radical approach does seem justified since no form of conservative therapy exerts any effect on the course of this condition The results of surgery will be discussed later

Signs and Symptoms—We have analyzed the data from 107 cases of abdominal aortic aneurysm seen at the New York Hospital during the 10 year period between 1945 and 1955 (Table III) The age incidence was as noted in Table IV Although signs and symptoms of this condition have been previously listed it is felt that analyzing them in greater detail may focus

TABLE III

Ratio of Recognized Abdominal Aortic Aneurysms to Total Admissions to The New York Hospital

Year	No of Admissions	No of Abdominal Aortic Aneurysms	Percent of Abdominal Aortic Aneurysms
1945	17589	6	0 03
1946	19079	4	0 0[illegible]
1947	20098	3	0 01
1948	20457	5	0 0[illegible]
1949	20914	7	0 03
1950	21944	14	0 0[illegible]
1951	21249	1[illegible]	0 06
1952	21500	13	0 06
1953	22644	21	0 09
1954	22824	15	0 0
1955		7 (incomplete)	

Total admissions 208 298
Total aneurysms 107
Percent of aneurysms 0 05%

TABLE IV

Age Incidence

Age	No of C
40–49	4
50–59	24
60–69	38
70–79	34
80–89	[illegible]
Average age 66 0	

attention on more precise and earlier diagnoses in the future In addition the present rarity of syphilis as an associated factor and other considerations may alter the findings For example this series was practically entirely in white patients there being only 4 negroes There were 89 males and 18 females In Dr Jere Lord s series 22 out of 23 were male Dr Lord has kindly consented to allow us to study an additional series of 23 patients not admitted to the New York Hospital In some respects this group is of particular interest since patients referred to a surgeon may differ from those in a mixed hospital population

The diagnoses were made or confirmed as follows Clinically—63 X ray—48 Laparotomy—16 Postmortem 21 The diagnosis was first made at laparotomy in 5 patients and first made at postmortem in 20 patients

TABLE V

Distribution of Pain

Abdominal	54
Low back	34
Legs	13
Chest	1
Groin	

TABLE VI

Symptoms

Pain	73
Constipation	17
Anorexia	13
Vomiting	13
Dyspnea	9
Diarrhea	8
Intermittent claudication	8
Throbbing sensation	6
Unconsciousness	4

Pain.—Pain was a major complaint but 34 patients did not suffer from it. Of the others 27 had severe pain, 7 described it as cramps, 13 complained of rather diffuse discomfort. Many had pain or other symptoms involving more than one area. In Dr. Lord's cases 21 out of 23 suffered from pain. This is to be expected in a selected group such as those referred to a surgeon. The distribution of pain was as seen in Table V. In some cases the pain as well as other symptoms ascribed to the aneurysm may in fact have been due to some other pathology, so that the symptoms herein listed as due to the aneurysm are approximate rather than absolute. Other symptoms were complained of as seen in Table VI. Seventeen patients remained asymptomatic. In Blakemore's series[1] 33.6 per cent were asymptomatic on admission. In Estes' series 30.4 per cent were asymptomatic.

Physical Signs.—The commonest physical sign was a mass which was noted in 69 patients. The mass was located as in Table VII. In 59 cases the masses were pulsatile. Some of these masses could be felt laterally as well as in the midline. The actual location of the aneurysm was found to be below the renal arteries in 58 cases and above the renal arteries in 12. In 15 cases the aneurysm involved the bifurcation and proximal iliac arteries. *Nineteen patients had 31 other aneurysms in various other arteries.* Five had additional aneurysms involving the thoracic aorta. None of our patients had evidence of the rare complication of associated aneurysm of the coronary arteries reported by Pukstinat.[3] His patient died from a rupture of an aneurysm of the abdominal aorta and was found to have six aneurysms of the right coronary artery associated with marked atherosclerosis. An

TABLE VII

Location of Mass

Umbilical area	17
Left upper quadrant	15
Epigastrium	14
Right upper quadrant	6
Left lower quadrant	6
Left flank	5
Right lower quadrant	4
Right flank	2
Hypogastrium	2

Total left side—26 *Total* right side—12 *Total* midline—33

TABLE VIII

Physical Signs

Mass	65
Tenderness on palpation	32
Weight loss	23
Bruit on auscultation	20
Diminished or absent pulses in groin or legs	11
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Edema of legs	5

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Roentgenographic Studies.—In 16 cases the diagnosis was made in the course of routine abdominal x-ray examinations. In 10 cases it was made in the course of intravenous pyelogram studies. In 23 cases it was more completely delineated by aortograms. It should be mentioned that at times A-P and lateral plates of the abdomen may show the outline of the dilated aorta clearly delineated by the calcific deposits while the aortogram shows only a smooth tube about the size of the aorta and without evidence of any pathology. This was very definite in the case of patient G. M. It was due to the formation of a firm thrombotic lining of the aneurysmal sac. In such cases the aortogram fails to be helpful while the diagnosis may be clear on physical examination and routine x-rays. Aortograms are not always uneventful. There have been cases of hypersensitivity reactions to the injected substance and of local hemorrhage, although these are few.

TABLE IX

Significant Laboratory Findings

Leukocytosis	30
Albuminuria	26
BUN retention	24
Anemia (usually hypochromic)	20

Laboratory Findings.—The most commonly encountered laboratory findings were as seen in Table IX. Evidence of renal disease was usually found associated with aneurysms above or involving the renal arteries. Aneurysms may dissect the walls of the renal arteries and this has produced uremia and hypertension.[5] No such cases were found in the present series from which dissecting aneurysms were excluded.

Additional Pathological Conditions.—Eighty three of these patients had definite evidence of atherosclerosis elsewhere in their arterial system. Seventy two had cardiovascular disease. This was predominantly atherosclerotic with or without hypertension. Fifty four had high blood pressure using the upper standards of normal as 150 maximum systolic and 90 maximum diastolic. Only four had diabetes mellitus. Twenty two suffered from gastrointestinal disease including 7 with cancer, 5 with peptic ulcers and 3 with inflammatory reactions such as gastritis, 4 with diverticulitis and 2 with gallbladder disease. These conditions frequently produced confusing symptomatology. Twenty two had genitourinary complaints including 7 with cancer of the bladder, 5 with nephrosclerosis, 3 with uremia, 2 with cancer of the prostate, 3 with renal infarcts and a variety of less significant conditions. Nineteen had evidence of pulmonary conditions, 10 of these had emphysema, the others varied greatly but included 4 with cancer of the lungs. Seven had evidence of neurological conditions including 5 with cerebral vascular accidents and with cerebral vascular disease without strokes.

Only 4 of these patients had serological or other evidence of syphilis and in only one instance was it believed that the aneurysm might have a syphilitic component. Even in this case syphilis was considered to be of doubtful importance in reference to the development of the aneurysm. This presents further evidence of the striking trend of the decreasing significance of syphilis as a factor in the development of aortic aneurysm. However the picture is not quite as clear cut in reference to abdominal aneurysm as it might appear at first glance. While it has long been recognized, as above mentioned, that thoracic aneurysms were predominantly syphilitic while abdominal aneurysms were less likely to be, early papers still listed syphilis as a cause or contributing factor in from 25 to 75 per cent of cases of abdominal aneurysms. It is doubtful that this represents the actual facts. Careful study of these papers indicates that in many instances the

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case however there was a sudden appearance of a nonpulsating mass on the day of the rupture All 17 of these patients died as a result of the rupture This has been the usual experience However with the advent of newer surgical technics we should re-examine the possibilities of this complication Logically the best method is prevention by excision and replacement of the aneurysmal segment prior to the rupture Even symptomless aneurysms may rupture so they do not guarantee safety but frequently the patient is not seen until the aortic wall is perforating and rupture is imminent or taking place It is common belief that it is then too late to operate but from now on it appears that in the best of surgical hands this will no longer be true and that an increasing number will be successfully operated upon The series reported by Goldowsky[10] is of interest in this regard He reported 15 cases of spontaneous abdominal aortic perforation verified by postmortem examinations He emphasized that contrary to common belief rupture of the abdominal aorta is not a cause of sudden death The patients in his series survived from 5 hours to 27 days Twelve patients survived more than 24 hours 8 patients more than 5 days It appears therefore that in each patient in this entire series there was *time* for surgical intervention In our series the survival period was shorter being from one to three days but in some there was ample time for surgical intervention Time is only one factor but has been generally thought to be too brief for such an approach Goldowsky's cases were reported in 1952 and most of them died prior to the era of aortic grafts but they are instructive In 10 the aneurysms were below the renal arteries and therefore might have been considered amenable to surgery Arteriosclerosis was marked and considered to be the etiological factor in each case No syphilis was found This was in contrast to the findings of Nixon who in 1911 reviewed the literature finding 223 cases of abdominal aneurysms of which 152 ruptured He reported that the majority had syphilis As pointed out above however that does not prove that syphilis was an etiological factor in these aneurysms unless proven pathologically in each case DeBakey has made notable strides in surgery for ruptured aneurysms having been able to operate successfully on 60 per cent of his cases See Table X

Type of Aneurysm —In 58 cases the type of aneurysm was satisfactorily classified by means of either autopsy or laparotomy In 32 patients the aneurysm was fusiform in type In 26 patients the aneurysm was saccular This was a high percentage of saccular abdominal aortic aneurysms as compared with most series Dissecting aneurysms usually start in the thoracic area and the dissection proceeds distally into the abdominal area It may also dissect toward the heart Dissecting aneurysms were not included in this study except for a single one which was confined to the abdominal aorta

Treatment —A total of 85 of these patients received no specific treatment

mere finding of a positive serological or historical evidence of syphilis but without histological evidence at the site of the aneurysm, led to the conclusion that any aortic aneurysm was wholly or partly due to syphilis In the light of present knowledge this was an unjustified assumption and it led to invalid conclusions This was especially aggravated by the fact that some of these reports came from the south where the percentage of negroes in the cases studied was high and where syphilis was extremely common among negroes at that time On the basis of pathological findings it does appear that there has been some decrease in the number of syphilitic abdominal aneurysms but that this is much less significant than might be concluded from a casual study of the figures alone For a review of this trend and the problems of analysis as outlined above the reader is referred to the papers of Kampmeier (1936) [6] Hubery & Pollock (1940) [7] Scott (1944) [8] Blakemore (1947) [9] Estes (1950),[2] and Goldowsky [10]

Mycotic Aneurysms—Mycotic aneurysms of the abdominal aorta are very rare and none were encountered in the present series It is probable that in the future they will be even rarer because of the widespread use of antibiotics Mitchell and Clairveaux[11] reported a case with rupture of a mycotic aneurysm of the abdominal aorta following pneumococcus endocarditis and they list 5 cases from the literature secondary to bacterial endocarditis The youngest patient on record to our knowledge was a child 7 years and 9 months old reported by Baginsky in 1908 [1] This patient had a streptococcal endocarditis and had an aneurysm of a subclavian artery as well as the abdominal aorta

Wilcox and Fisher[13] described a case of particular interest A 54 year old woman developed a streptococcus viridans subacute bacterial endocarditis Emboli occluded the femoral arteries of both legs Following heavy penicillin therapy her temperature returned to normal clubbing of her fingers disappeared and the spleen was no longer palpable The patient nevertheless did not feel well She had pains in the legs hips and lower abdomen and a persistent pulse about 120 per minute Her blood cultures were persistently negative Thirty four days after she became afebrile a pulsatile mass appeared below the umbilicus Twenty days later she died of a rupture of this aneurysm in a matter of minutes At autopsy bacteria were found in the wall of the aneurysm but none could be found in the blood or the heart valves

Rupture of Aneurysms of the Abdominal Aorta—Rupture is the most dreaded terminal event in the history of these aneurysms unless surgical intervention is undertaken Seventeen aneurysms in the present series ruptured In 9 of these the aneurysm had been diagnosed before the rupture in periods ranging from several months to 2 years In 7 patients the diagnosis of aneurysm was made only when it ruptured In none of these cases was an increase in the size of the mass noted before it ruptured In one

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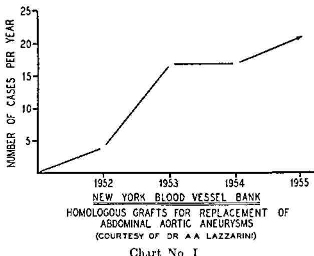
with rupture of that artery The other death occurred five weeks after operation from an infection of the anastomosis of the right common iliac artery with rupture and hemorrhage One living patient is seriously ill with heart failure

In recent years this problem has been vigorously attacked by numerous surgeons of note The introduction of fine wire into the aneurysmal sac to encourage reinforced clot formation with electrical stimulation was developed and studied with great care by Blakemore and his coworkers The wrapping of the outer walls of aneurysms by cellophane and other fibroplastic stimulating materials has been carried out by numerous surgeons While the results in certain specific patients have apparently been encouraging many of them have died at the time of operation or soon after so that the proof that the prognosis is on the average better for the patient is difficult to establish and in our opinion lacking The over all operative mortality in Blakemore s series of 1954 was 37 2 per cent—of these rupture was the cause in 19 1 per cent (20 cases) Nine of these showed evidence of rupture before operation 3 ruptured at operation and 8 ruptured post operatively 18 1 per cent died of other causes including heart failure and thrombosis If wrapping is attempted Blakemore prefers to use a strong plastic cloth such as nylon or vinyon N

Types of Operation

1 Aortic occlusions proximal to aneurysm (no longer used)
2 Thrombo-endaorterectomy and wrapping (no longer used)
3 The production of thrombosis within the aneurysm by means of wiring with or without endothermy (no longer used)
4 Partial or complete external reinforcement or wrapping (used by some surgeons when because of patient s condition or technical difficulty graft is not feasible)
5 Resection and replacement—favored today
   a) Homograft
   b) Prosthesis of dacron orlon vinyon N or other plastic in the developmental phase

Not all of the patients who have had the wiring procedure have done poorly For example Patient P H age 77 was operated on in 1950 for an abdominal aneurysm at which time silver wire was introduced In 1951 a second operation was performed when more silver wire was inserted Both operations were performed by Dr Blakemore In 1955 the patient was alive and active and was admitted to The New York Hospital for a ureteral calculus which was passed Incidentally he has also survived a myocardial infarction with development of auricular fibrillation left bundle branch block and periodic cardiac decompensation



NEW YORK BLOOD VESSEL BANK
HOMOLOGOUS GRAFTS FOR REPLACEMENT OF ABDOMINAL AORTIC ANEURYSMS
(COURTESY OF DR A A LAZZARINI)

Chart No I

for their aneurysm. This reflects the fact that most of them were seen in an era when surgical treatment was not available. Chart No I (courtesy of Dr Abel Lazzarini) shows the increase in interest in the surgical approach in the past 4 years as indicated by the request for grafts from the Blood Vessel Bank.

The Surgical Approach.—If surgery is to be elected it must be justified by evidence that the risk is less than the prognosis without surgery.

Fifteen of these patients had resection and graft. Nine of these were successful. Failures were due to rupture of the anastomoses in two cases, uremia in 2 cases, leakage of the aneurysm in one, and rupture preoperatively in one. Four cases were wrapped with plastic material. The results were successful in 3 cases. One died 1 day postoperatively of pulmonary edema and shock.

Two patients were treated by the Blakemore wiring procedure with results as follows: One is still alive after 5 years, one died 3 days postoperatively, one patient had his aorta ligated below the renal arteries but developed gangrene of the legs and died.

In Dr Jere Lord's series subjected to surgery, 11 were resected and grafted, of which 5 have been successful, 3 were treated by wrapping, of whom 2 are alive (1 month and 3½ years postoperatively). Two were injected with sodium dicetylphosphate, of whom one is living.

Dr S W Moore has operated on 11 patients for abdominal aortic aneurysm of whom 9 have been successful with satisfactory postoperative courses up to two years. One patient died in the hospital. He had a history of 2 myocardial infarctions. He was operated on for a ruptured abdominal aneurysm and after this died of thrombosis of the left common iliac artery

with rupture of that artery The other death occurred five weeks after operation from an infection of the anastomosis of the right common iliac artery with rupture and hemorrhage One living patient is seriously ill with heart failure

In recent years this problem has been vigorously attacked by numerous surgeons of note The introduction of fine wire into the aneurysmal sac to encourage reinforced clot formation with electrical stimulation was developed and studied with great care by Blakemore and his coworkers The wrapping of the outer walls of aneurysms by cellophane and other fibroplastic stimulating materials has been carried out by numerous surgeons While the results in certain specific patients have apparently been encouraging many of them have died at the time of operation or soon after so that the proof that the prognosis is on the average better for the patient is difficult to establish and in our opinion lacking The over all operative *mortality in Blakemore's series of 19.4 was 37 2 per cent—of these rupture* was the cause in 19 1 per cent (20 cases) Nine of these showed evidence of rupture before operation 3 ruptured at operation and 8 ruptured postoperatively, 18 1 per cent died of other causes including heart failure and thrombosis If wrapping is attempted Blakemore prefers to use a strong plastic cloth such as nylon or vinyon N

Types of Operation

1 Aortic occlusions proximal to aneurysm (no longer used)
2 Thrombo-endaorterectomy and wrapping (no longer used)
3 The production of thrombosis within the aneurysm by means of wiring with or without endothermy (no longer used)
4 Partial or complete external reinforcement or wrapping (used by some surgeons when because of patient's condition or technical difficulty graft is not feasible)
5 Resection and replacement—favored today
   a) Homograft
   b) Prosthesis of dacron orlon vinyon N or other plastic in the developmental phase

Not all of the patients who have had the wiring procedure have done poorly For example Patient R H age 77 was operated on in 1950 for an abdominal aneurysm at which time silver wire was introduced In 1951 a second operation was performed when more silver wire was inserted Both operations were performed by Dr Blakemore In 1955 the patient was alive and active and was admitted to The New York Hospital for a ureteral calculus which was passed Incidentally he has also survived a myocardial infarction with development of auricular fibrillation left bundle branch block and periodic cardiac decompensation

While a few surgeons still use wrapping in some cases where resection seems impractical, the interest today is definitely in the direction of resection of the aneurysm with the substitution of a graft of either homologous aorta or a prosthesis of plastic material such as vinyon N or orlon. This type of procedure is still fraught with considerable risk but the great progress of the past 5 years indicates more successful use in the future. Saccular aneurysms are frequently attached by a pedicle which may permit lateral clamping and suture. This procedure often produces excellent results and has been reported by many surgeons including Dubost and Dubost[14] Bahnson[15] and DeBakey and Cooley and Creech.[16, 17] The sac should be removed if possible. If a whole sac is left in place the danger of infection is considerable. If a portion of the sac is adherent to a vital area such as the inferior vena cava, it may be necessary to leave it in place. This has been successful in many cases.

So far as we can determine, the first successful homologous graft to replace a fusiform aneurysm of a human aorta was performed by Dubost on March 29, 1951.[18] The graft was functioning and in good condition when reported 3 years later.[14] This was a graft of considerable size extending from the level of the renal arteries to include the upper portion of the right common iliac artery and was attached to the left common iliac artery. Dubost and Dubost[14] emphasized that the aorta near an aneurysm is often thickened, friable, and indurated with calcareous patches or medial necrosis. It is therefore easily cut by sutures producing secondary ruptures. They mentioned ruptures occurring on the 29th day and six months after resection. They also point out that if syphilis is present, antibiotic treatment should certainly be given prior to surgery and while we must agree to this the effect on the outcome of any specific operation may be doubtful, especially in the case of abdominal aneurysms which are so rarely syphilitic today.

The number of homografts which have been performed since that of Dubost cannot be determined because they are now being undertaken in many areas of the world today. The degree of over all success is also difficult to determine but on the basis of our knowledge from wide travel and work in various countries, it can be stated that to this date there is a great variation in the results. This is to be expected with any new, highly technical procedure and is based on lack of experience with this operation, unsatisfactory preparation and preservation of the grafts, and lack of criteria of indications and contraindications for this type of procedure as well as all of the usual problems of surgery in the elderly patient with widespread atherosclerosis and frequently other diseases. Outstanding reports have come from the clinics of Bahnson who in 1954[15] reported 14 patients in whom he had performed aortic homografts, of whom 11 were alive and well

TABLE X

Operative Results—(DeBakey)

	Total Operation	Mortality
Non ruptured cases	14[illegible]	10%
Ruptured cases	[illegible]	40%

Recent Figures—Mortality

Non ruptured cases	5 out of [illegible]1 cases (%)
Ruptured cases	4 out of 11 cases (3[illegible]%)

(one required amputation of one leg) and DeBakey[16, 17] In 1955 DeBakey et al reported the following results Forty nine abdominal aneurysms had been resected and grafted Of those who recovered 36 were reported to be in excellent condition while none were in poor condition Thirteen died 7 of coronary disease 4 of renal failure early 2 died later of unspecified causes In all but six cases the aneurysm involved the bifurcation which had to be resected The death rate of the operation was 16 per cent below 60 years of age and 32 per cent above 60 years of age In 13 patients orlon cloth prostheses had been used to replace aortic bifurcations with satisfactory results DeBakey presented additional figures before the Annual session of the American Heart Association in October 1955 They are as seen in Table X

One of the technical steps of major concern has been the prolonged occlusion of the aorta with the secondary ischemia of the tissues of the legs We have observed several examples of failure of adequate restoration of circulation after this procedure with loss of one or both legs This has occurred in patients who had demonstrated marked evidence of occlusive arteriosclerotic disease prior to operation Therefore proper account of this risk should be taken in the preoperative study of the patient DeBakey and Cooley state that for aneurysms below the renal arteries arrest of circulation with an aortic clamp for 120 minutes has not produced residual ischemic changes They have used two procedures to reduce this risk 1) Lumbar sympathectomy as part of their operation and 2) Injection of 10 mg of heparin into the aneurysm just before occluding the aorta to retard thrombophilic effects of retarded blood flow in the distal vascular bed It is our belief that this dosage is probably on the low side for this purpose but recognize the undesirability of producing too generalized a bleeding tendency during such an operation They claim that most patients actually had improved circulation to their lower extremities after the operation These results certainly justify much wider use of this technic by properly equipped surgical teams

For successful widespread use of homografts a highly efficient blood vessel bank with a large source of suitable grafts is a requisite This paper will not attempt to discuss the technic or functioning of such a bank It appears

that the demand may well outstrip the supply even in large cities especially since in many cases bifurcations are needed In smaller communities and for emergencies prostheses of synthetic material should be available if practical Their use has been explored by numerous workers notably Blakemore[1] and Debakey [17] Blakemore has used 37 denier 144 x 90 strands per square inch of vinyon N cloth In dogs sacrificed 19 to 153 days postoperatively he found all prostheses to be encased in fibrous tissue 1–5 mm in thickness The inner surface was covered with a thin translucent film consistent with multiple layers of flattened cells and collagen fibers with fibroblasts growing through the interstices of the cloth Of the first 4 cases in man using this material one died in 5 days from uremia and one died of hemorrhage from rupture of a thinned posterior wall proximal to the line of suture Two patients did well and were discharged with good pulsations in the arteries of the feet As mentioned above, DeBakey reported 13 such cases using orlon and nylon with good results While at present homografts are favored the use of such prostheses should be developed They offer the great practical advantages of ease of preparation and preservation and they can be woven or cut to fit almost any forseeable demand in terms of vessel length or arrangement

Careful preoperative studies make a satisfactory analysis possible in most cases However the decision as to whether to attempt a surgical procedure or not has sometimes been difficult without a laparotomy

Postoperative Care —Our observations and review of cases leads us to believe that in some instances the technical surgery has been excellent but a leg or a life has been lost because of lack of attention to certain details during the postoperative period We therefore suggest that particular attention be paid to the following

1 In most patients the feet should be 6 inches below the heart level to encourage return of good arterial circulation On many surgical services a common procedure is to elevate the foot of the bed and thought is not given to the physiological needs after this procedure

2 Prophylactically heparin should be instilled into the aneurysm or the distal iliac arteries when the proximal artery is occluded to minimize the risk of sludge or thrombus formation

3 If there is evidence that the circulation is poor this may well be due to sludge or soft clot formation Heparin should be started immediately It should preferably be given into the femoral arteries by continuous drip or in daily amounts of 300 mg per 1000 cc of 5 per cent dextrose This will encourage disintegration of the sludge or clot rather than consolidation of it and may well save an extremity This may be continued for 8 to 10 days or an oral anticoagulant may be substituted after the first 3 to 4 days The use of anticoagulants is not universal for this purpose but appears to be increasingly accepted

4 Peripheral vasoconstricting drugs should be avoided unless vitally needed to keep the blood pressure up They may further endanger extremities already in jeopardy from poor circulation

5 Unless there is an overbalancing contraindication fluids must be administered at a high level of 2500 cc or more a day since dehydration encourages thrombosis

6 The electrolyte balance should be controlled carefully

7 Antibiotic therapy should be administered prophylactically

8 Gastric suction should be used freely to prevent distention, paralytic ileus and pressure on the new graft site

9 Active exercise of the lower extremities should begin with the return of consciousness

10 The use of an oscillating bed is justified especially if the circulation of the legs is impaired

Indications for Resection and Graft for Abdominal Aortic Aneurysms — There are some justifiable differences of opinion regarding the indications and contraindications for this type of surgery There are surgeons who believe that any aortic aneurysm should be operated upon regardless of level or type Others feel that if the aneurysm is above the renal arteries or involves the renal arteries the results will not justify the surgery Our present indications for operation are as follows

1 A patient who has an abdominal aortic aneurysm and whose general condition seems good enough to tolerate surgery of this magnitude

2 A palpable pulsating mass in or near the midline of the abdomen especially if this is increasing in size under observation —This makes the operation urgent

3 Pain in this area intermittent or persistent especially if severe enough to require narcotics

4 Evidence of rupture or leakage constitutes an emergency indication for operation

5 Anteroposterior and lateral x ray plates showing the calcific outline of an aneurysm

6 An aortogram demonstrating an aneurysm which appears operable

7 Availability of a suitable graft or prosthesis

8 A surgical team with sound experience with this type of surgery

9 The indications are the same regardless of the etiology of the aneurysm although the outlook for syphilitic aneurysms (fortunately rare) is poorer than for the other types

Indications for Great Caution or Operation Only Under Unusual Circumstances —

1 Recent or repeated myocardial infarction

2 Definite evidence of coronary insufficiency Some surgeons suggest

the simple operation of wrapping the aneurysm if progression forces an operation in the face of either of these two contraindications

3 Extreme hypertension e g 240/140 which should be reduced prior to operation if possible

4 Marked arterial insufficiency of the lower extremities with risk of or impending gangrene

5 Involvement of the renal arteries with renal insufficiency

Absolute Contraindication —The presence of another disease which will inevitably kill the patient within a short time

Results of surgery —The immediate results appear to justify the surgical approach when the above outlined criteria are utilized The results appear to maintain a favorable balance throughout a two year follow up period There are an insufficient number of patients who have been followed for a longer period to make final conclusions possible regarding a long range comparison with untreated cases

Conclusions

1 Technical advances in the surgical treatment of abdominal aortic aneurysm justify further examination of this approach

2 The great majority of abdominal aortic aneurysms are arteriosclerotic, syphilitic and mycotic aneurysms are now very rare

3 The life expectancy is poor with 85 to 95% of the patients dying within 5 years of the diagnosis This type of aneurysm should be regarded as seriously as cancer

4 The symptoms and signs are varied and often masked by other pathological processes but their careful analysis frequently leads to the correct diagnosis

5 Roentgenography studies both with standard techniques and visualization with contrast media are usually helpful in confirming the diagnosis

6 Each case should be analyzed in terms of suitability for surgery and the great majority can be successfully operated upon

7 Various types of surgical approach have been tried but today the emphasis is on resection of the aneurysm and its replacement by a graft

8 The present choice is a homologous aortic graft but plastic grafts using Nylon Orlon and Vinyon are coming into use and it is possible that they will be used in the majority of cases in the future

9 The indications *reasons for caution and contraindications* have been analyzed

10 Rupture of an abdominal aneurysm is the most common fatal complication but with modern technique and prompt action an increasing number of these cases are being successfully operated upon

11 The technical advances of urgery have greatly improved the outlook for the treatment of the aneurysm it elf but it must be borne in mind that most of these patients are over 60 years of age and have widespread vascular disease or other malignant disea e from which more than 50% of them will die within 5 years

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DISCUSSION

DR WILLIAM D STROUD (Philadelphia) I would like to a k Dr Wright if it is true that surgeons are reconstructing the renal arteries Ca es which I have sent to

surgeons which have involvement of the renal artery have very rarely been as he said operative but I have heard that some cases have been operated upon with reconstruction of the *e renal arteries*

DR RUDOLPH H KAMPMEIER (Nashville Tennessee) I was very interested in the figures in Dr Wright's tables In comparing these tables with ancient history an analysis of abdominal aneurysms I made some twenty years ago an interesting fact appears on the incidence as related to age

At the present time as you see from Dr Wright's tables on incidence practically all of the cases fall between sixty and eighty years of age

In seventy three cases I analyzed twenty years ago at Charity Hospital only one patient was above the age of sixty five In fact only eight of the seventy three were above the age of fifty five Fifty nine were under forty five years of age Six deaths from aneurysm of the abdominal aorta occurred between twenty and twenty five years of age

The age incidence at that time certainly fell into that in which one encountered the *saccular aneurysms of the aorta*

In a goodly proportion of these instances there was good pathologic evidence for syphilis I have wished to point out this difference in the age incidence then as compared to now What is the meaning of such a sharp contrast in age incidence before twenty years ago and the age incidence at the present time? It means that the syphilitic aneurysm has been replaced by the arteriosclerotic aneurysm for obvious reason —the universal treatment of syphilis and the increased life span I make this point merely to keep the clinical perspective unclouded

DR CLAUDE J FORKNER (Boston) I would like to ask Dr Wright how his clinical evidence of aortic abdominal aneurysm compares with observation at autopsy I think that perhaps many cases of atherosclerotic abdominal aneurysm go along unrecognized and without symptoms for many years Hence such patients may not be seen in the hospital as often as in doctors' offices Therefore such cases may not be *listed in the ordinary classification as it appears on hospital records* and may not appear in ordinary autopsy reports unless a particular interest was present either in the internist or the pathologist

DR THOMAS FINDLEY (Augusta) I just wonder if Dr Wright or anyone else here has had any experience with an ancient method of controlling symptoms due to external pressure from an aneurysm I think the method was first advocated by Malpighi and it was commonly employed during the seventeenth and eighteenth centuries It consists simply of repeated venesection Although it seemed silly we tried it in some eighteen or twenty intractable cases with dramatic remissions in 80 to 90 per cent of them lasting as long as a year or two We simply did phlebotomies for 2–5 days until the circulating hemoglobin dropped to about 8 grams and they were then allowed to recover spontaneously The pressure in the brachial artery does not change I have no idea what happens

I simply bring this up because Dr DeBakey in New Orleans indicated to me that he thought this problem of abdominal aneurysm was pretty well solved and that the next exciting development would be in the thorax where of course pressure symptoms may often be intractable and not amenable to surgery

DR ROBERT W WILKINS (Boston) I would like to ask if there was hypertension in the patients who had an aneurysm extending as high as the renal arteries as opposed to those who had it below that point and second did hypertension play a discernible role in the instance of rupture? We ordinarily think of hypertension certainly in the case of dissecting aneurysm as the most important contributing factor

Dr. James M. McGuire (Cincinnati): I would like to comment on an interesting patient with an arteriosclerotic aneurysm of the abdominal aorta. This 50 year old individual was operated upon because of the presence of a pulsating and painful mass in the mid abdomen five years ago. At operation there was a markedly dilated and paper thin aneurysm of the abdominal aorta originating just below the renal artery and extending to the pelvis. Fresh and old hemorrhage in the surrounding tissues immediately adjacent to the aneurysm indicated a slow leak. The surgeon, deeming the condition inoperable, closed the incision without doing anything. Needless to say the prognosis was given to the family as being poor. I was agreeably surprised that this patient has done extremely well for the past five years without any disagreeable symptom, although the palpable aneurysm pulsates as vigorously as ever.

We have encountered interesting physical findings in two male patients with arteriosclerotic aneurysms which ruptured, the diagnosis of both being confirmed at autopsy. In these patients a soft palpable mass feeling like an inguinal hernia was palpated in the left inguinal canal. At autopsy the masses proved to be hemorrhage dissecting along the vas deferens.

Dr. F. Tremaine Billings, Jr. (Nashville): Dr. Wright mentioned that in some of these patients there were several other aneurysms in the same patient. I wonder if he has seen any with aneurysms of the coronary arteries.

We just had a patient who died of coronary artery occlusion following the replacement of the aneurysmal abdominal aorta with a graft. Two fairly large aneurysms were present in the coronary arteries, both of which were very completely occluded.

Dr. Robert L. Levy (New York): I have seen a number of Blakemore's patients and I merely want to add that when, for one reason or another, excision with replacement has been impossible, a palliative procedure consisting of the placing of a constricting band either of tissue or plastic has served helpfully on occasion.

Dr. Irving S. Wright (Closing): I find myself in the same predicament as the former speaker: to answer all of the questions I would have to give another paper. I think the questions which were asked have been for the most part answered in the manuscript.

In answer to Dr. Stroud, it is true that surgeons are beginning to attempt reconstruction of the renal arteries, and there have been a few successes. But it is a pretty difficult thing to do, and many of the cases have not been successful, renal failure having developed within several days.

Sometimes the surgeon is confronted with most unusual problems, such as happened with Dr. Jere Lord. He placed a clamp on the aorta at a reasonable distance below the renal arteries, but as close as he thought would be safe. As he applied the clamp a new aneurysm popped out just above the renal artery, probably due to the sudden double hammerhead of pressure which took place. This was a most disconcerting thing to have happen. But this aneurysm was rather accul r, so he was able to remove it by excision and revision of the wall then going on with the original procedure.

Dr. Kampmeier's figures were of great interest to us, along with many others, and reference is made to his work in our manuscript. Unfortunately I did not have time to refer to it in this presentation.

One of the most interesting findings has been the change in pathogenesis from syphilis to an arteriosclerosis, and, as you would expect, a corresponding change in age incidence.

However, in analyzing the series of the past, I am rather inclined to believe that the fact that a man had syphilis and had an aneurysm was often considered as evi-

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THE DIFFERENTIAL DIAGNOSIS OF MASSIVE PULMONARY EMBOLISM

By L. WHITTINGTON GORHAM, M.D.

NEW YORK

There will first be presented the study of 50 fatal cases of massive pulmonary embolism correlating pathological and clinical findings. (I am indebted to Dr John G Kidd, Professor of Pathology at Cornell University, for the privilege of reviewing this material.)

The cases selected all showed large obstructive lesions involving the main stem of the pulmonary artery and one or two of its principal branches in 40 cases (80 per cent). In five instances the right branch alone was blocked and in five others the left branch alone was occluded. Fatal cases with only smaller vessel emboli and infarcts were excluded.

The patients averaged 60 years of age (oldest 83, youngest 18); there were 29 males and 21 females; there were 14 medical cases and 36 surgical cases. The clinical diagnosis was incorrect in 26 instances (52 per cent), coronary occlusion being wrongly diagnosed eight times and given as an alternate diagnosis three times. There was evident difficulty in excluding myocardial infarction, therefore, in 11 cases (22 per cent).

The onset in all 50 cases was sudden, with signs of shock, pallor, sweating and weak, rapid, thready pulse. All showed a marked disturbance of respiration; some were cyanotic. 28 (56 per cent) survived over 15 minutes. Contrary to the statements sometimes made, typical cardiac pain was present in nine patients (18 per cent); substernal pressure or pain in six and precordial pain in three. There was also typical radiation to the left shoulder in two and to the interscapular region in one of these nine cases. The emboli in all nine patients occluded more than one branch and even extended back into the right ventricle in two cases, similar to illustration. The coronary arteries were all widely patent in these patients, with minimal atherosclerosis. There is considerable evidence to indicate that the cardiac type of pain suffered is due to tension on the wall of the pulmonary artery rather than to the hypothetical pulmono coronary reflex through the vagus.

In 24 (48 per cent) of these 50 cases with massive emboli there was associated embolization of smaller vessels with infarcts; all 24 of these infarctions preceded by days or weeks the final fatal closure of a large vessel. Emboli in small vessels do not kill as a rule. They may produce no symptoms at all or may extend to the pleura causing the well known axillary pain on

From The Public Health Research Institute of The City of New York, Inc., New York, N. Y.

dence that his aneurysm was on the basis of syphilis This was particularly confusing in some other papers which came out of the South where there were large Negro wards and a high percentage of syphilis In the light of our present thinking this conclusion does not hold If syphilis is not established in the aortic wall as determined by pathological examination the mere fact that a man has a positive Wassermann fails to prove a relationship It is a possibility but absolute proof is essential for diagnosis

Regarding Dr Forkner s question of the clinical evidence versus pathological evidence as is true in many other fields of medicine the pathologist uncovers some case of abdominal aortic aneurysm which the clinician misses If the clinician is keen the batting average in this I think is better than in most diseases but in some cases there is a dilatation or a perforation of an aneurysm back toward the spine and with very little evidence anteriorly so that one cannot pick up the clinical manifestations very easily

Some of these cases have ruptured the diagnosis having been made at death On the other hand recently we have seen a patient who was operated on for a rupture of his known aneurysm only to find it intact but that he had suffered a perforation of a diverticulum of his colon

The pathological cases at the New York Hospital were included in this series

Dr Wilkins in reference to hypertension and the renal arteries I would not think you could say that a sufficiently sound study has been carried out to demonstrate this point clearly It is true that a fairly high percentage of the cases which ruptured did have hypertension and that when some of the renal arteries were blocked those patients usually had hypertension prior to death But I think this is an angle which needs much more complete study than we have given it

Dr Findley the purpose of repeated phlebotomy was an attempt to bring the pressure down One of the patients I mentioned improved in the hospital and we let him go along for two more years We did periodic phlebotomies and also gave him hypotensive drugs In some of the cases it seems as if some of the new hypertensive drugs will react rather similarly in decompressing the pressure to some degree apparently

It is worth while to try to reduce the strain but as to whether the long range outlook is affected I have grave doubts It may be temporarily ameliorated

Regarding Dr Johnson McGuire s question about other types of surgery as you all know there has been a great variety of procedures tried There have been wiring and wrapping procedures and injection of chemical substances and various other types of surgery In general the trend now is in the direction of grafts of various kinds I should not be surprised if it becomes more and more toward the use of synthetic prostheses because they can be tailored to the need of the patient to a greater degree and with greater ease than trying to have a set up of homografts which fit every possible need But this is something for the future

The by pass procedure has been used in some cases but it is really just getting started I think it will be very interesting to see what the future brings in that

In reference to the aneurysm of the coronary artery in combination with an abdominal aortic aneurysm if you have such a case it ought to be reported since there are only two or three cases in the literature One by the way had six aneurysms of his coronary arteries in addition to abdominal aortic aneurysm It is an extremely rare combination It did not occur in our series although we looked hard for it

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The cases selected all showed large obstructive lesions involving the main stem of the pulmonary artery and one or two of its principal branches in 40 cases (80 per cent). In five instances the right branch alone was blocked and in five others the left branch alone was occluded. Fatal cases with only smaller vessel emboli and infarcts were excluded.

The patients averaged 60 years of age (oldest 83, youngest 18); there were 29 males and 21 females; there were 14 medical cases and 36 surgical cases. The clinical diagnosis was incorrect in 26 instances (52 per cent), coronary occlusion being wrongly diagnosed eight times and given as an alternate diagnosis three times. There was evident difficulty in excluding myocardial infarction, therefore, in 11 cases (22 per cent).

The onset in all 50 cases was sudden with signs of shock, pallor, sweating and weak, rapid thready pulse. All showed a marked disturbance of respiration; some were cyanotic. 28 (56 per cent) survived over 15 minutes. Contrary to the statements sometimes made, typical cardiac pain was present in nine patients (18 per cent): substernal pressure or pain in six and precordial pain in three. There was also typical radiation to the left shoulder in two and to the interscapular region in one of these nine cases. The emboli in all nine patients occluded more than one branch and even extended back into the right ventricle in two cases, similar to illustration. The coronary arteries were all widely patent in these patients, with minimal atherosclerosis. There is considerable evidence to indicate that the cardiac type of pain suffered is due to tension on the wall of the pulmonary artery rather than to the hypothetical pulmono coronary reflex through the vagus.

In 24 (48 per cent) of these 50 cases with massive emboli there was associated embolization of smaller vessels with infarcts; all 24 of these infarctions preceded by days or weeks the final fatal closure of a large vessel. Emboli in small vessels do not kill as a rule. They may produce no symptoms at all or may extend to the pleura causing the well known axillary pain on

From The Public Health Research Institute of The City of New York, Inc., New York, N. Y.

deep breathing cough bloody sputum and perhaps a friction rub These signs of pulmonary infarction are often mentioned as findings of diagnostic importance which accompany massive pulmonary embolism It has even been said that the larger the embolus the larger the infarct Nothing could be farther from the truth The lungs in massive pulmonary embolism as a rule show no parenchymatous changes except moderate atelecta is and edema which was in our series 14% of the cases Infarcts almost always small do occur as stated in 48 per cent of cases In our series of 24 infarcts only 11 (46 per cent) were diagnosed correctly clinically At autopsy 12 (50 per cent) small silent infarcts were found with no overlying pleurisy

In the 50 cases studied bloody sputum was recorded only three time friction rub four times and axillary pain nine times Thrombophlebitis was diagnosed clinically seven times and found at autopsy in 30 cases

We see clearly therefore that there are two distinct types of clinical reaction to the lodging of an embolus in a pulmonary artery Embolism and infarction are not synonymous terms The symptoms produced will depend upon the size of the embolus its consistency the size of the vessel occluded the degree of obstruction produced and the speed with which closure occurs

No disease is perhaps more often diagnosed incorrectly than massive pulmonary embolism There are numerous reports in the literature which indicate that an accurate diagnosis is made on the average in about 50 per cent of cases *This paper will endeavor to demonstrate why* there is such a high percentage of error and what if anything can be done to reduce it

Until Herrick s[1] classical contribution appeared in 1912 sudden deaths were almost invariably and erroneously ascribed to pulmonary embolism or to so called acute indigestion Since that date the pendulum has swung in the other direction and sudden deaths which occur at the pre ent time are prone to be attributed to coronary occlusion While the differentia tion of massive pulmonary embolism from coronary occlusion may be rela tively simple in certain in tances it may on the other hand present the greatest difficulty because of the striking similarity of the symptomatology in the two conditions Massive pulmonary embolism may be ushered in by unusual symptoms leading to various diagnoses *but* the greatest number of incorrect diagnoses in all eries reported involve myocardial infarction

In 1934 Churchill while discussing the physical examination of patients with pulmonary embolism aptly points out that it is exceedingly difficult to find an adequate clinical analysis of what really takes place The sudden unexpected event of impending death in a patient who is well on the road to recovery after a surgical operation tends because of its tragic nature "to color the observations with inaccuracies

In spite of the dearth of accurate comprehensive examinations of such patients there are to be found in the literature isolated case reports which contain one or more of eleven different physical signs

The distension of the pulmonary artery in massive pulmonary embolism has been well established by experimental ligation in animals and by direct observation upon patients subjected to pulmonary embolectomy

In spite of the fact that Kirschner[3] who reported the first successful embolectomy in 1924 described two important physical signs resulting from acute pulmonary hypertension i e a sharply accented second pulmonic sound and an increase of cardiac dullness to the right little attention was paid to these in the diagnosis of pulmonary embolism

Approximately eleven years were to elapse however before McGinn and White[4] made their outstanding and classical contribution to the diagnosis of pulmonary embolism This appeared in 1935 under the now well known title of Acute Cor Pulmonale Although this paper was the first to establish definitely the value of the electrocardiogram in the diagnosis of pulmonary embolism it was also the first publication to describe adequately and to emphasize the importance of most of the physical signs which may be encountered in this condition These were pulsation in the second left interspace an accented pulmonary second sound a pseudo- or pleuro pericardial friction rub distended jugular veins increased cardiac dullness to the right of the sternum and a gallop rhythm best heard at the pulmonic area

Pulsation in the second left interspace may also be seen in congenital heart disease in mitral stenosis in Ayerza s disease (primary pulmonary arteriosclerosis) and possibly in very thin chested normal young individuals

A greatly accented pulmonary second sound was first recorded in two cases in 1913 by Schumacher[5] who emphasized its importance in the differential diagnosis of massive pulmonary embolism when considering embolectomy Left ventricular failure may cause accentuation of the pulmonary second sound but is usually accompanied by bilateral basal rales of edema In the early stages of massive pulmonary embolism there are no rales unless over an infarct which is apt to be unilateral

The presence of a pericardial friction sound which tends to be located high on the left side of the chest may cause great confusion in the diagnosis between pulmonary embolism and myocardial infarction unless one knows that a pseudo or pleuro pericardial scratchy sound may occasionally occur in massive pulmonary embolism The author s personal interest in this physical sign dates to 1926 when a man was seen with substernal pain pericardial friction rub and EKG changes The diagnosis of myocardial infarction was made Since an injury to the femoral vein by a large paper

hook had occurred three weeks before death, the possibility of accidental death and double indemnity life insurance was raised as an argument for obtaining an autopsy. Post mortem showed pulmonary embolism and no evidence of myocardial infarction. The puzzling fact that a pericardial friction rub had been heard in this and one other patient was not fully explained until 1935 when McGinn and White [4] having detected it in two of their cases suggested that it might be due to a markedly dilated pulmonary artery rubbing against the pericardium.

A systolic murmur accompanied by a thrill at the pulmonic area was reported as early as 1882 by Litten.[6]

The mechanism by which such a murmur is produced would appear to be a partial stenosis of the pulmonary artery caused by the embolus. In those rare cases where a long coiled embolus extends from the right ventricle through the pulmonary valve into the main stem of the pulmonary artery it is easy to understand that a systolic murmur with a thrill might develop due to stenosis and that perhaps also a diastolic murmur of pulmonary insufficiency might be detected. Litten described both of these murmurs in massive pulmonary embolism caused by echinococcus cysts.

The diastolic murmur in massive pulmonary embolism first described by Litten has been confirmed by only one observer—Einar Key [7] in 1929. Kirschner [3] 1924 believed it might occur but never detected it in a case of massive pulmonary embolism.

The interscapular bruit has never been reported in the literature. Dr George P. Herrmann,[8] Professor of Medicine at the University of Texas, is entitled to the credit for first reporting this finding in a patient and for explaining its mechanism. He suggested that it is due to a rider thrombus found at autopsy at the bifurcation of the pulmonary artery. This observation was confirmed in the patient by another able clinician, Dr. M. R. Nejmanek.

I am indebted to Dr. Herrmann for the following report and for the permission to publish it.

A 52 year old woman was operated upon for repair of a large ventral hernia. After 24 hours sudden extreme dyspnea developed with respiration 50, signs of shock and death 43 hours later. Sputum was slightly bloody on the 2nd day but no axillary pain, pleural friction or phlebitis were present. A definite systolic bruit was heard in the back between the scapulae.

Autopsy showed a massive embolus filling the right pulmonary artery and extending into the branch supplying the right upper lobe. A photograph of this embolus in situ is shown in figure 1. An infarct was present in this lobe of the lung. Thrombophlebitis in the right femoral vein was found. The coronary arteries were widely patent with no sclerosis and no evidence of myocardial fibrosis.



Fig 1

The diminished expansion and reduced respiratory murmur when an embolus obstructs either the right or the left branch of the pulmonary artery alone has only been described by one observer, viz Fichelter [9] in 1932

When the right heart fails in massive pulmonary emboli m the detection of increased cardiac dullness to the right of the sternum is a physical sign of supreme importance Schumacher [5] 1913 Kirschner [3] 1924 and McGinn and White [4] 1935 all refer to this physical sign

Engorgement of the neck veins represents important evidence of right sided heart failure White observed it in six of his reported cases of pulmonary embolism

A gallop rhythm heard most distinctly over the second and third left interspace was described in 1935 by McGinn and White [4] They observed this sign in cases 2 4 8 and 9 of their report Two of these patients recovered so it is impossible to state how large a vessel must be occluded in order to produce this sign The one case (#4) which came to autopsy showed a large embolus at the bifurcation Case #9 which had severe substernal pain and oppression dying in $2\frac{1}{2}$ hours did not come to autopsy although the clinical picture was that of a major branch occlusion Cases #2 and #8 which recovered may have had temporary occlusion of a major branch with subsequent breaking up of the embolus and passage onward deeper into the lung It is probable that gallop rhythm occurs for the most part with obstruction of the main stem or the main branches

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porary sharply defined radiolucency found early in small pulmonary infarction It eem quite logical that if the pulmonary arterial blood flow in a small ve el i uddenly obstructe l by an embolu the pulmonary parenchyma normally upplied with blood but now deprive l of circulation woul l be for a brief time more ra lio lucent than normal In one or two in tances I have fancie l I have een th same thing with post mortem proof of small emboli m

Colonel Carl Tempel at Fitz immon Army H pital howed me a patient who had had a large emboli m of a main br nch of the pulmonary artery with urvival for a hort perio l of time During that period of urvival x ray picture of hi che t showed an amazing difference in the ra liolucency of that i l lue to lecrea e l bloo l fl w through it compare l with the other i le

I woul l like to a k Dr Gorham if in any of the urviving patient with a block of th main pulmonary artery on ne si le did he ee pulmonary tuberculo i ul e quently develop on that ide

Scott Hanlon and Ol on did ome extremely intere ting experiment t sh w that in rea ed oxygen supply to a limite l part of the lung led to rapid progre i n of tuberculo i in that place The e experiment were done on monkeys with ligation an l/or ana tomo i of v temi ve el to pulmonary ve el before an l after intr v i u inj ction of tubercle bacilli

S m fifteen ye rs ago I h l a patient with exten ive pulmonary arteriovenou aneury m throughout one lung Since pneumonectom wa refu ed the main l ranch of the pulmonary artery to the right lung as ligated He made a nice recovery to the ome ten year later of pulmonary tuberculo i apparently starting and pro gres ing un loul tedly mo t ver ly in the right l ung hich had been getting pre sumably nly well oxyg nated bloo l through the bronchial arterie

DR FRA IS C W D (Philadelphia) I have been ver much intere te l ever ince I wa in me lical chool in th y tolic murmur which appear in the ec n l or thir l left interspac in y t le I remember that I w tol l that on of the lou l murmur wa a functional murmur an l nother ne which I coul l lar ly r wa rganic It bothered me con ler bly

I ran acr a rather inter t ng po i l explanation or e tim ly ccident I n I was doing me operation on a log coronarie The dog tarte l getting extra y toles so I put my tethoscope n the heart t ee what t our le l k Whil I wa l tening i l ul y tol e murmur appeared Then I foun l out much to my ir tere t that this murmur c ul l b produced by the e lg of the tethoscope ver lightly in lenting the pulmonary artery The minute I rel eve l this pre ure th murmur di appeare l

I therefore have u pected alth ough I have never prove l it that th functional pulmonary y tolic murmur in young peopl who have no heart li a e due to th rib slightly in lenting the pulmonary artery becau e alm t all of tho e young people re flat che ted If you look very carefully in uch pat ent n xpirati on ou will e a pul ati n n th area If the patient take a full breath ar l l l t the murmur li ppear

Thi murmur will al be h ar l po i l lue to a imilar me h ni m if the pul mon ry a t ry i dilate l an l i impinging on a rib

I woul l r f ome f the e sy tolic murmurs l ear l after pulm nary emboli m are n t l to a ute dilation of the pulmonary artery hich u e it to pre again t the thir l ril

DR IR IN S WRIGHT (New York) I woul l l ke t a k Dr Gorham if he ould tell u how m ny of th e emboli hich were fatal were preced l by previ u emboli

The fact that a portion of a large embolus obstructing the main stem of the pulmonary artery may be broken off and passed on into a smaller vessel seems to be indicated by a unique observation of Kirschner[3] in 1924 While observing a patient apparently dying from massive pulmonary embolism he noted that a *red arterial wave seemed to pass suddenly* over the pallid cyanotic face for a few moments only A short time later the same phenomenon appeared a second time The explanation given was that a dislodged piece of the obstructing embolus temporarily permitted an additional amount of freshly oxygenated blood to pass through the lung to the left heart from whence it was pumped to the patient s face

Although many of the foregoing signs have been seen and recorded by competent observers at various times it has been impossible for me to discover that anyone has urged the systematic search for them in all cases of sudden death

Until this is done and their presence or absence recorded we shall not know their true incidence and importance I suspect however that a higher percentage of correct diagnoses of pulmonary embolism could be made if the eleven signs mentioned were routinely sought for Perhaps in order to fix this idea in the medical mind we might imitate Sir William Osler s catchword of the renal sextet in nephritis by calling these sign The Embolic Eleven

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DISCUSSION

DR JAMES J WARING (Denver) Dr Thomas some year ago a Scandinavian I think it was Westermark called attention to the roentgenographic change a tem

In answer to Dr. Wright's question as to how many of the fatal pulmonary emboli were preceded with clinically detectable smaller emboli (in other words, a warning embolus), or whether on autopsy they showed evidence which suggested that there had been previous emboli which might have been a warning if they had been picked up, I would say there were twenty-four cases of infarction in the series of 50 patients. There were eleven cases which were diagnosed clinically because of thrombophlebitis or because of pleural pain or bloody sputum in two or three instances. But there were twelve silent infarcts of the twenty-four which nobody had even suspected, and the reason they did not suspect them was that they were not large enough to extend to the pleura to cause pain and there was no bloody sputum raised.

In answer to Dr. Craige's question: Why is this type of obstruction of the pulmonary artery so much more lethal than a simple obstruction by the surgeon when he does a pneumonectomy, that is, he can occlude the artery and the patient seems to get through that perfectly well, or sometimes that has been done with a balloon and the patient survives. I would say that it has been shown experimentally that you have to occlude about 75 to 80 per cent of the pulmonary arterial circulation in order to cause death.

Dr. Richmond Moore some years ago at the Rockefeller Institute did some very interesting experiments in which he placed a suture about the pulmonary artery of a dog, then closed the chest, and by pulling on the suture he could produce all the signs of pulmonary embolism and death.

I did not enter into the question of the mechanism of pain and the mechanism of death which are really the interesting part which this study is leading up to. Many cardiologists feel that these patients die because of the reflex action upon the coronary circulation, but as I said Katz's work indicates that the vagal fibers are dilators rather than constrictors, and there is some very good evidence to show that the substernal pain which these patients have develops not as a result of impaired coronary circulation but because of tension on the wall of the artery.

In 1[illegible] a German investigator [illegible]chelte operated on one of these cases of pulmonary embolism under local anesthesia while the patient was conscious. He palpated and pulled the pulmonary artery and the patient complained of substernal pain and pressure. He thought that probably this pain was due to Wanddehnung which is stretching on the wall. So it is quite possible that one might undertake an experimental approach to this problem which I would like to do one day, similar to work I did years ago on the coronary vessels by putting tridirectional tension on the wall and proving that you can produce heart pain by tension without ischemia.

which were recognized either clinically or could be deduced from the pathological studies

There are figures which are of some interest in regard to this Following surgical operative procedures if a person who has a recognized embolus receives no therapy to combat future emboli he has about a 20 per cent chance of dying of a second or third or other pulmonary embolus The e figures vary from different clinics but in most clinics which have made a study of it they are of some significance

That leads to the next statement which you might surmise I am going to make Despite the fact that I would like to see Dr Gorham s series enlarged and studied further I am even more interested in trying to prevent it from becoming larger There is increasing evidence that particularly in patients who have had repeated thrombophlebitis a history of pulmonary emboli is very common This occurs especially following surgery in the lower abdominal area — such as herniorraphy Using anticoagulants properly makes it possible to do a pretty good job prophylactically

Dr Ernest Craige (Chapel Hill North Carolina) I would like to ask Dr Gorham if he has any thoughts upon the reason the e emboli are so much more lethal than the obstruction of a similar artery by the surgeon when he does a pneumonectomy or by the experimenter with the introduction of a balloon One can obstruct an artery apparently without much serious effect by either of these methods

Dr A Carlton Ernstene (Cleveland) I think Dr Gorham s statistics indicate the importance of the emergency which is created by one of these pulmonary incidents The fact that so many of the patients have died within a period of fifteen minutes certainly speaks for itself

I believe his observations also point out a weakness in our teaching program for residents Certainly when one of these accidents occurs things rapidly degenerate into utter confusion and this probably is the explanation for the lack of description of the physical signs which are present prior to the patient s death Often the chief of the service gets word of what has been going on with an announcement that his patient has expired

It seems to me therefore that we should emphasize to our residents the fact that these physical signs are present and that it is worth while to make an effort to record them

Dr L Whittington Gorham (In Closing) Dr Waring your comment was whether we found tuberculosis in any portion of the lung where there was a thrombus occluding a major branch or one of the subbranches is that it?

Dr Waring Either way and of course in a long surviving patient It takes a little time for tuberculosis to develop

Dr Gorham Of course I was studying patients who had massive emboli with major occlusions 80 per cent of them were in the main stem and the right or left branch in addition So the very cases you are inquiring about I did not study I just put those to one side

There was no tuberculosis however in any of these 50 cases which died suddenly About half of them had in addition small emboli with infarcts and half of those infarcts had not been diagnosed

Dr Wood spoke about the dilatation of the pulmonary artery I think without doubt the murmur may be explained on the basis of dilatation Just as in younger people the second pulmonary heart sound is louder than the aortic second up to the age of eighteen years so one would expect in these thin persons especially if you get the light in a proper direction and make a few little cross hatches with your fountain pen and then look carefully at the second left intercostal space that you might see pulsation which otherwise you might readily miss

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